H03762-22-P024944

MAY 1991 VOL 66 NO 5

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

565 Allergic rhinitis *C J Trigg, R J Davies*
567 Routine measurement of blood pressure in schoolchildren *P N Houtman, M J Dillon*

Original articles

569 Oxygen saturation and breathing patterns in infancy. 1: Full term infants in the second month of life *V A Stebbens, C F Poets, J R Alexander, et al*
574 Oxygen saturation and breathing patterns in infancy. 2: Preterm infants at discharge from special care *C F Poets, V A Stebbens, J R Alexander, et al*
579 Airway response to exercise and methacholine in children with respiratory symptoms *J B Clough, S A Hutchinson, J D Williams, et al*
584 Is low birth weight a risk factor for asthma during adolescence? *D S Seidman, A Laor, R Gale, et al*
588 Long term follow up of renal function in IgA nephropathy *U B Berg*
593 Renal histological changes in relation to renal function and urinary protein excretion in IgA nephropathy *U B Berg, S-O Bohman, U Widstam-Attorps*
598 Changes in body composition and energy expenditure after six weeks' growth hormone treatment *J W Gregory, S A Greene, R T Jung, et al*
603 Infantile meningitis in England and Wales: a two year study *J de Louvois, J Blackbourn, R Hurley, et al*
608 Increasing incidence of coeliac disease in Sweden *H Ascher, I Krantz, B Kristiansson*
612 Glucose tolerance in cystic fibrosis *Susanne Lanng, Birger Thorsteinsson, Gunna Erichsen, et al*
617 Mechanisms of gastro-oesophageal reflux in cystic fibrosis *S Cucchiara, F Santamaria, M R Andreotti, et al*
623 Computed tomography of the brain in kwashiorkor: a follow up study *K C Househam*
627 How mothers keep their babies warm *C J Bacon, S A Bell, E E Clulow, et al*
633 Delay in diagnosis of childhood asthma and its influence on respiratory consultation rates *Ian Charlton, Kevin Jones, John Bain*
636 Septicaemia and adrenal haemorrhage in congenital asplenia *M P Dyke, R P Martin, P J Berry*
638 Malignant osteopetrosis: hypercalcaemia after bone marrow transplantation *P S M Rawlinson, R H A Green, A M Coggins, et al*
639 Genetic aspects of admissions to a paediatric intensive care unit *D R FitzPatrick, C H Skeoch, J L Tolmie*
641 Teratogenic effect of carbamazepine *V Vestermark, S Vestermark*

Challenges

643 Providing medical care for children *David Hull*

Personal practice

647 Supraventricular tachycardia: diagnosis and current acute management *Janice A Till, Elliot A Shinebourne*

Current topic

653 Persistent infant crying *I St James-Roberts*

Personal view

656 District handicap teams in England: 1983-8 *M C O Bax, Kingsley Whitmore*
665 **Sister journals—United States** *Harvey Marcovitch*
666 **Letters to the editor**
667 **Book reviews**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

CP 24944

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Editors: Bernard Valman, Malcolm Chiswick
Associate Editors: Derek Johnston, Michael Silverman, Brian Wharton
Statistical Adviser: Michael Healy
Technical Editor: Sue Heels
Editorial Assistant: Jacinta Marshall

EDITORIAL COMMITTEE

F Cockburn
T J David
M J Dillon
M E Garralda
H L Halliday
I M Hann
I A Hughes
J W Keeling
C R Kennedy
S W Lenton
J K Lloyd
H Marcovitch
N McIntosh
P J Milla
L Polnay
P Raine
P T Rudd
J F N Taylor
R M Winter
J E Wraith
Editor, *BMJ*

NOTES TO CONTRIBUTORS Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

NOTICE TO ADVERTISERS Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *Archives of Disease in Childhood* is published monthly. The annual subscription rates are £127 inland and £140 overseas (USA $208). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All inquiries however must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All inquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

COPYRIGHT © 1991 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Published by the British Medical Association, Tavistock Square, London WC1H 9JR and printed in England by The Devonshire Press Ltd, Torquay.

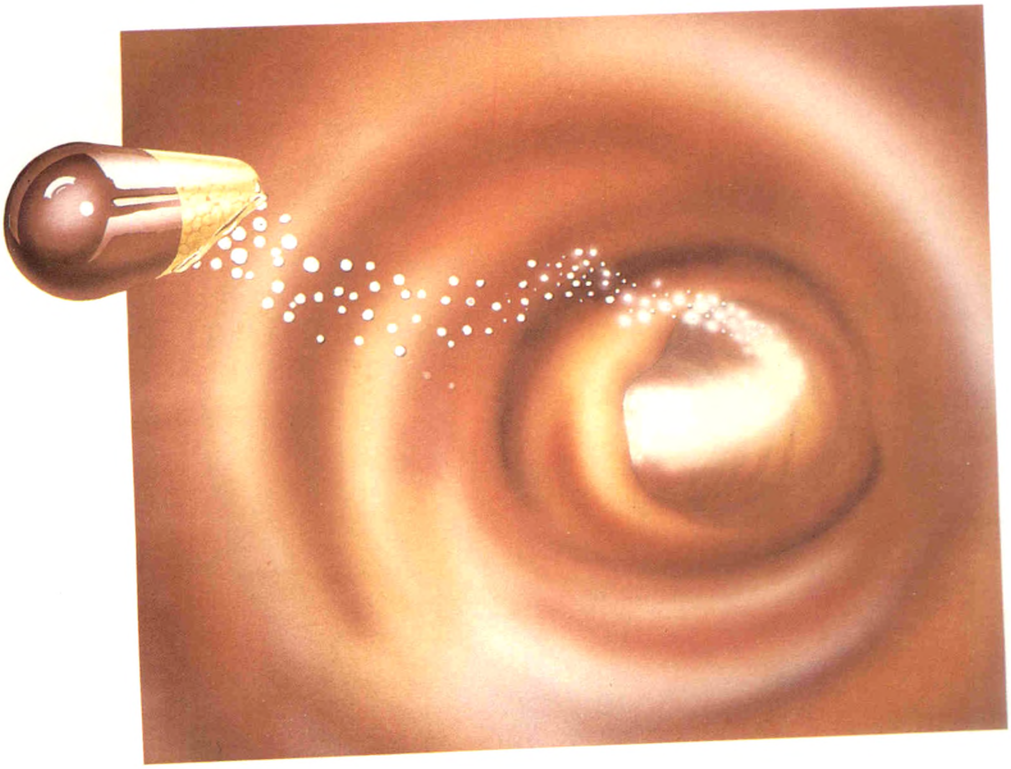
Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0003-9888

[illegible] G.G.

PROGRESS

In The Management Of Cystic Fibrosis



creon®
pancreatin

[redacted]

chives of Disease in Childhood 1991; **66**: 565–568

ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Allergic rhinitis

Prevalence and epidemiology

The prevalence of allergic respiratory diseases in the popula- on is increasing. Fleming and Crombie showed that in England and Wales, the number of patients attending general practitioners' surgeries with rhinitis doubled between 1974 and 1982 with a peak prevalence in the 15–25 year age group (4%).[1] The reason for this increase is uncertain, but it may well be associated with socioeconomic factors. Strachan showed that there was a strong inverse relationship between hay fever and family size.[2] Furthermore, position in the household also influenced the development of rhinitis, firstborn children being at greatest risk. Both relationships were independent of the social class of the father. During recent years, fewer children in families and improvements in hygiene may have reduced the incidence of viral cross infection between siblings at a critical age. Strachan suggested that such cross infection might be protective against rhinitis; this is a novel hypothesis as previous studies have implicated viral infections in the pathogenesis of both rhinitis and asthma. Frick *et al* showed that the onset of allergic disease in infants with allergic parents was related temporally to preceding viral infections such as respiratory syncytial virus and parainfluenza.[3] Furthermore, several investigators have shown that total concentrations of circulating IgE are raised during the acute phase of iral infections.[4 5]

ITANCE OF ATOPY

genetic studies suggest that atopy (the ability of a o produce high concentrations of IgE directed nmon allergens) may be inherited, carried on 11 as an autosomal dominant characteristic penetrance.[6 7] Certainly most allergic children g family history of allergy, and concordance for of allergy is increased in monozygotic compared gotic twins.[8]

NMENTAL INFLUENCES

nvironmental factors probably contribute to the sen- n of an allergy prone subject in early life. Children spring in Scandinavia have an increased risk of birch n rhinitis,[9] and grass pollen has the same effect in the ed Kingdom.[10] Sibbald and Rink, however, have ntly shown that rhinitis in non-atopic subjects is also ciated with birth during the summer months, suggest- that other factors, such as winter respiratory tract infection at a time when transferred maternal immunoglobulin concentrations have fallen below protective levels, may promote the development of rhinitis. Parental smoking is certainly associated with wheezing in children,[12] but also with risk of rhinitis. In a large study in rural Sweden the relative risk of rhinitis increased to 1·8 in children who lived in damp homes and had parents who smoked.[13] The effects of damp and passive smoking were synergistic, neither factor being a significant independent risk. Modern energy efficient 'tight' buildings may encourage the growth of house dust mites and moulds, thus increasing environmental exposure to potential allergens.[14]

Industrial environmental pollution is also likely to be a contributory factor. Comparative studies between developed and developing countries suggest a lower prevalence of allergic diseases in the latter.[15] Furthermore, studies of urban and rural populations suggest that urban dwellers are more prone to rhinitis.[16] Pollen grains in urban areas are contaminated by pollutants, and such deposits on inhaled pollen may act as adjuvants to sensitisation.

Nasal responsiveness

It is not surprising that nasal responsiveness has similar characteristics to bronchial responsiveness, given that the nose is contiguous with the rest of the respiratory tract. Nasal airways resistance can be measured and increased non-specific nasal responsiveness can be induced with agents such as histamine and other mediators, although the range of responsiveness in rhinitis is less clear cut than that of bronchial responsiveness in asthmatic patients.[17] The lower repeatability of measurements of nasal airways resistance compared with that of forced expiratory volume in one second (FEV_1) together with the absence of a smooth muscle constrictor response, contributes to this difference. The response to methacholine seems to be entirely secretory, in contrast to the highly correlated methacholine and histamine responses in the lower airways. The absence of smooth muscle in the nose almost certainly accounts for the difference.[17]

Early and late phase allergic responses may also be induced in the nose. Late phase responses occur in about half the patients between two to eight hours after challenge, but only produce small rises in nasal airways resistance.[18] The late phase response is less pronounced than in the lower airway, firstly because there is no smooth muscle, and secondly because the response may be masked by the nasal cycle in which there is an increase in nasal airways resistance in alternate nostrils every two to four hours.[19]

Pathogenesis

MAST CELLS

Studies of the nasal mucosa in patients with rhinitis have shown that total numbers of mast cells are increased compared with patients without rhinitis.[20] Furthermore, there is a significant increase in the numbers of mast cells and eosinophils during the pollen season.[21] There is also evidence that the number of circulating mast cell/basophil progenitors is increased in such patients and that their numbers fall during the pollen season, suggesting the possibility of recruitment to the site of allergic inflammation.[22] It is likely that atopic subjects are predisposed to produce the cytokines necessary for basophil/mast cell and eosinophil differentiation.[22] Plaut *et al* showed that murine mast cells triggered by cross linkage of Fc$_\varepsilon$RI receptors secrete interleukins 3 (basophil activation), 4 (IgE synthesis), and 5 (eosinophil activation), which suggests that there is a positive feedback mechanism amplifying the inflammatory response.[23]

Other mast cell products released in the acute phase after allergen administration include histamine, prostaglandin D$_2$, kinins and tryptase, which are likely to be responsible for many immediate symptoms.[24] The release of these mediators shows the features of priming—that is, repeated allergen challenge within the same day is followed by an augmented response.

Mast cell heterogeneity has been found in nasal polyp tissue, with tryptase positive mucosal type cells predominat-

[redacted]

contribute to the inflammatory features of the late phase response.

T CELLS

There seems to be an imbalance in cytokine production from T cells in atopic subjects, who have a tendency to produce more of interleukins 4 and 5 and less interferon gamma. The numbers of dendritic cells at the surface of the nasal epithelium are increased in rhinitics and these may bind allergenic peptides. Interaction of these dendritic cells with T cells may promote differentiation towards the helper type of T cells (Th2) that produce interleukins 4 and 5, which promote B cell IgE production and eosinophil activation, respectively.[30] In situ hybridisation studies show that T cells from atopic and asthmatic patients express messenger RNA for interleukins 4 and 5.[30 31]

Effect of treatment

VASOCONSTRICTORS

α-Adrenergic agonists such as ephedrine act on the smooth muscle of the venous system in the nasal mucosa. They are highly effective in immediately increasing nasal patency. There is a low risk of rebound congestion with compounds such as xylometazoline and naphazoline, but fears of 'rhinitis medicamentosa' have limited their use to one to two weeks periods only.[32]

1 Fleming DM, Crombie DL. Prevalence of asthma and hayfever in England and Wales. *BMJ* 1987;**294**:279–83.

2 Strachen DP. Hayfever and household size. *BMJ* 1989;**299**:1259–60.

3 Frick OL. Effect of respiratory and other virus infections on IgE immunoregulation. *J Allergy Clin Immunol* 1986;**78**:1013–8.

4 Welliver RC, Kaul TN, Ogra PL. The appearance of cell-bound IgE in respiratory tract epithelium after respiratory syncytial virus infection. *N Engl J Med* 1980;**303**:1198–202.

5 Perelmutter L, Phipps P, Potvin L. Viral infection and IgE levels. *Ann Allergy* 1978;**41**:158.

6 Cookson WOCM, Hopkin JM. Dominant inheritance of atopic immunoglobulin E responsiveness. *Lancet* 1988;**i**:86–8.

7 Cookson WOCM, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989;**ii**:1292–5.

8 Edfors-Lubs ML. Allergy in 7000 twin pairs. *Acta Allergologica* 1971;**26**:249–85.

9 Bjorksten F, Suoniemi I, Koski V. Neonatal birch pollen contact and subsequent allergy to birch pollen. *Clinical Allergy* 1980;**10**:581.

10 Morrison-Smith J, Springett VH. Atopic disease and month of birth. *Clinical Allergy* 1979;**9**:153–7.

11 Sibbald B, Rink E. Birth month variation in atopic and non-atopic rhinitis. *Clin Exper Allergy* 1990;**20**:285–8.

12 Cogswell JJ, Mitchell EB, Alexander J. Parental smoking, breast feeding and respiratory infection in the development of allergic disease. *Arch Dis Child* 1987;**62**:338–44.

13 Andrae S, Axelson O, Bjorksten B, Fredricksson M, Kjellman N-I M. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. *Arch Dis Child* 1988;**63**:473–8.

14 Korsgaard J. Mite asthma and residency. *Am Rev Respir Dis* 1983;**128**:231–5.

15 Cookson JB. Prevalence rates of asthma in developing countries and their comparison with those in Europe and North America. *Chest* 1987;**91**(suppl):97–103.

16 Miyamoto T, Takajugi S, Suzuki S, Takadoro K, Muranaka K. Allergy and changing environments: industrial/urban pollution. In: Pichler WJ, ed. *Progress in allergy and clinical immunology*. Toronto: Hogrefe and Huber, 1989:265–70.

17 Corrado O, Gould CAL, Kassab JY, Davies RJ. Nasal response of rhinitic and non-rhinitic subjects to histamine and methacholine: a comparative study. *Thorax* 1986;**41**:863–8.

18 Fergusson H, Davies RJ. Late phase nasal responses—reviewed and revisited. *Respiratory Medicine* 1990 (in press).

19 Eiser N. The hitch-hikers guide to nasal airway patency. *Respiratory Medicine* 1990;**84**:179–84.

20 Gomez E, Corrado O, Baldwin DL, Swanston AR, Davies RJ. Direct in vivo evidence for mast cell degranulation during allergen induced reactions in man. *J Allergy Clin Immunol* 1986;**778**:637–45.

21 Lozewicz S, Gomez E, Clague J, Gatland D, Davies RJ. Allergen induced changes in the nasal mucous membrane in seasonal allergic rhinitis: effect of nedocromil sodium. *J Allergy Clin Immunol* 1990;**85**:125–31.

22 Denburg JA, Dolovich J, Harnish D. Basophil mast cell and eosinophil growth and differentiation factors in human allergic disease. *Clin Exper Allergy* 1989;**19**:249–55.

23 Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE. Mast cell lines produce lymphokines in response to cross-linkage of FcεRI or to calcium ionophores. *Nature* 1989;**339**:64–7.

24 Togias A, Naclerio RM, Proud D, *et al*. Studies on the allergic and non-allergic nasal inflammation. *J Allergy Clin Immunol* 1988;**81**:782–90.

25 Kawabori S, Denburg J, Irani A, Schwartz LB, Dolovich J. Characteristics of mast cells in nasal polyps. *J Allergy Clin Immunol* 1990;**85**:253.

26 Lozewicz S, Greenwood L, Walls AF, Gomez E, Davies RJ. Mast cells in human bronchi are heterogeneous with respect to granule esterase activity. *Respiratory Medicine* 1990;**84**:499–502.

27 Gomez E, Corrado O, Davies RJ. Histochemical and functional characteristics of the human nasal mast cell. *Int Arch Allergy Appl Immunol* 1987;**83**:52–6.

28 Lozewicz S, Gomez E, Chalstrey S, Gatland D, Davies RJ. The time-course of cellular infiltration in the nasal mucosa during the immediate allergic reaction. *Thorax* 1988;**43**:810P.

29 Bascom R, Pipkorn U, Gleich J, Lichtenstein LM, Naclerio RM. Effect of systemic steroids on eosinophils and major basic protein during antigen challenge. *J Allergy Clin Immunol* 1986;**77**:246.

30 Ricci M, Rossi O. Dysregulation of IgE responses and airway allergic inflammation in atopic individuals. *Clin Exper Allergy* 1990;**20**:601–10.

31 Kay AB. Lymphocytes in asthma. *Respiratory Medicine* (in press).

32 Davies RJ, Ollier S, Cundell DR. Drug treatment for nasal allergy. *Clin Exper Allergy* 1989;**19**:559–69.

33 Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol* 1989;**83**:905–12.

34 Henocq E, Rihoux J-P. Does reversed-type anaphylaxis in healthy subjects mimic a real allergic reaction? *Clin Exper Allergy* 1990;**20**:269–72.

35 Thomson NC. Nedocromil sodium: an overview. *Respiratory Medicine* 1990;**83**:269–76.

36 Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respiratory Medicine* 1990;**84**(suppl A):19–23.

37 Thomas KE, Greenwood L, Murrant N, Cook J, Devalia JL, Davies RJ. The effects of topical fluticasone propionate on allergen-induced immediate nasal airways response and eosinophil activation: preliminary results. *Respiratory Medicine* 1990;**84**(suppl A):33–5.

38 Dolovich J, Anderson M, Chodirker W, *et al*. Fluticasone propionate: a large multicentre trial. *Respiratory Medicine* 1990;**84**(suppl A):31–2.

Routine measurement of blood pressure in schoolchildren

Undergraduate and postgraduate medical students learn that the measurement of blood pressure is part of routine clinical examination. This would seem a reasonable assertion; however, as will be shown in this article, it requires a thorough understanding of the factors involved in the production of a valid measurement in order to interpret blood pressure meaningfully in children.

Apart from research purposes, the endpoint of measuring blood pressure must be to identify some pathology. That pathology may be a disease causing secondary hypertension, in which case it is important that the clinician should know how to deal efficiently with abnormal findings, probably referring those with severe hypertension to tertiary centres.[1] Otherwise it may be perhaps a more subtle tendency towards essential hypertension, in which case there should be provision for long term follow up, including the difficult period around adolescence, and later, when transfer to adult care is necessary. In both cases, it is important neither to miss a treatable condition nor create unnecessary anxiety to parents and child by failing to recognise normality. This article addresses some of the factors leading to valid assessment of blood pressure.

When to measure blood pressure

The most important hurdle to overcome in relation to blood pressure measurement in children concerns the decision actually to take the blood pressure. The recent working party of the British Hypertension Society did not recommend the routine screening of the paediatric population for blood pressure.[2] Blood pressure in children is very variable,[3] and so regression to the mean, which has long been a problem in trials of antihypertensive treatments in adults,[4] is likely to cause even greater problems in children. Thus although the phenomenon of 'tracking' of blood pressure allows some prediction of later hypertension,[5] the correlation coefficients between initial and follow up blood pressure measurements in a number of studies are relatively low and insufficiently consistent to allow predictions of future blood pressure levels from initial recordings, especially in young children.[6 7]

The situation becomes more unclear when considering the child with a family history of hypertension. While it would seem prudent to follow up a child with a strongly positive family history, the power of observations made before adolescence is debatable.[8] The position may be different during adolescence when there is probably greater overall predictive value, but traditionally this is a period when medical input is at a minimum.

At the other end of the range, there seems little doubt that blood pressure should be measured in all children presenting to clinicians when ill or when illness is suspected. This would be expected practice in adults, and there is no reason why it should not be applied to children. The following groups of children should also have regular routine blood pressure measurements because of the known association between certain pathological states and hypertension: those with any form of renal or cardiovascular disease, urological abnormalities, meningomyelocoele, diabetes mellitus, and neurofibromatosis. Also those with headaches, visual symptoms, facial palsy, acute neurological disease, hypercalcaemia, lead poisoning, and acute hypovolaemia. Drug treatment with steroids, sympathomimetics, the contraceptive pill, and intravenous administration of blood products or saline must be monitored by blood pressure recordings.[9]

Circumstances of measurement

The blood pressure should be taken in a situation which produces least anxiety. The phenomenon of 'white coat' hypertension in adulthood is clearly applicable to children.[10] Some explanation of the procedure, appropriate to the child's age, is certainly advisable as in younger children the non-invasive nature of the experience is not always appreciated, and the procedure can actually be perceived as quite painful, even if performed properly. The room must be at a reasonable ambient temperature,[11] and the child should have been sitting quietly for a few minutes (for example, the recording should not be performed directly after the assessment of power in all four limbs!).

The technique that is most practicable for widespread clinical application is that using a conventional, well

[redacted]

appropriate normal range of values. Blood pressure clearly increases with age, although not dramatically so in the school age group until puberty, and all the available charts make reference to age, either directly or indirectly.

The charts currently most used in the English speaking world are those produced by the Second Task Force on Blood Pressure Control in Children from Bethesda, in the United States,[13] which relate blood pressure directly to age. Despite stressing the importance of multiple measurements the charts are based, for reasons of study design, on first readings only and this makes interpretation difficult.[20] These data make some allowance for the size of the individual, which is important as most children with raised blood pressure with respect to age will be obese[21] and further management will be altered accordingly. It may be more appropriate altogether, in view of the known influences of body size on blood pressure, to relate blood pressure to height directly[16] and charts exist for this.[22] Which ever charts are used, it is probably valuable to have 'normograms' available in the clinical setting.

In conclusion, the chances of achieving valid and efficient blood pressure measurements are improved if the sources of

THE VERY PALATABLE FACTS ABOUT PREJOMIN

Prejomin is the prescribable protein hydrolysate that's completely free from lactose and milk protein residues.

So it will suit a far greater number of your hypersensitive patients.

But just as important, its taste will suit them as well.

And with babies or infants, a hypoallergenic formula can only be as good as it tastes.

The Prejomin combination of nutrients has proved itself eminently acceptable to them again and again.

While its proven efficacy will make it equally acceptable to you.

Prejomin. The palatable solution to the dietetic management of chronic diarrhoea and food intolerances.

milupa
prejomin
Hypoallergenic semi-elemental formula for infants and children
Free from milk protein, lactose, sucrose, galactose, fructose and gluten

milupa
Experts in
Infant Nutritio

lupa Ltd., Milupa House, Uxbridge Road, Hillingdon, Uxbridge, Middlesex UB10 0NF. Telephone: 081-573 996

Some infants
are ahead of their time.

Fortunately, so are we.

Cow & Gate has been looking after the nutritional needs of infants for over 90 years. During that time, we've created the widest range of formulas and foods for normal infants and those with very special needs.

The low birth weight baby is one of them.

Our Low Birth Weight Formula was specially created to provide higher energy and nutrient levels, at a lower volume than might otherwise be obtained from breast-milk or standard infant formula –

This formulation was one of the first designed to meet the guidelines set out by ESPGAN, the European Society of Paediatric Gastroenterology and Nutrition.

What's more, Cow & Gate Low Birth Weight Formula achieves good calcium retention and still offers the lowest osmolality of any low birth weight formula available today.

Cow & Gate Low Birth Weight Formula. Well-absorbed. Proven well-tolerated.

And just one of an ever

[redacted]

Archives of Disease in Childhood 1991; **66:** 569–573

ORIGINAL ARTICLES

Oxygen saturation and breathing patterns in infancy. 1: Full term infants in the second month of life

V A Stebbens, C F Poets, J R Alexander, W A Arrowsmith, D P Southall

Abstract

Overnight 12 hour tape recordings were made of arterial oxygen saturation (SaO_2, pulse oximeter in the beat to beat mode) and abdominal wall breathing movement on 67 healthy, full term infants between the ages of 29 and 54 (median 39) days. The median baseline SaO_2 during regular breathing was 99·8% (range 97·0–100%). Fifty four infants (81%) had shortlived episodes during which SaO_2 fell to 80% or less (desaturation); the median rate was 0·9 desaturations/hour, and the median duration of each desaturation was 1·2 seconds. The 97th centile value for the duration of all episodes in which SaO_2 fell to ≤80% was 4·0 seconds. The frequency of desaturations was significantly higher, and their duration significantly longer, when the breathing pattern was non-regular rather than regular. The percentage of apnoeic pauses (≥4 seconds in duration) followed by a desaturation was higher during non-regular than regular breathing; it was particularly high during periodic breathing.

A knowledge of normal variability of baseline measurements of oxygenation and of the relationship between oxygenation and breathing patterns in infants is essential to the use of pulse oximetry in clinical practice.

Pulse oximetry was introduced into clinical practice about 10 years ago. Since then many validation studies have been done with pulse oximeters made by different manufacturers. Some of these studies in infants have shown a close correlation with arterial oxygen saturation (SaO_2) measured by co-oximetry.[1–4] It has been shown, however, that correlations might vary depending which pulse oximeter was used.[5]

In addition to its clinical use in monitoring oxygenation, pulse oximetry may be of value in cardiorespiratory physiology.[6] It is a non-invasive technique, and can provide immediate information about sudden changes in arterial oxygenation.

In the clinical management of patients with cardiac or respiratory failure, or both, when accurate information about baseline measurements of oxygenation is particularly valuable, pulse oximeters are generally used in an 'averaging' mode. In such modes the displayed values are calculated as an average of the saturation measurements at each pulse during the preceding 2–15 seconds. For research and diagnostic purposes, however, it is possible to use some instruments without averaging several pulses—that is, in a 'beat to beat' mode. This offers advantages: immediate information is available about any changes in oxygen saturation; these changes, combined with an assessment of the photoplethysmographic pulse waveforms, indicate when false saturation values are being caused by movement or other artefact; and, finally, artefactual signals are not averaged with non-artefactual signals.

Previous studies using pulse oximetry in infants have shown that sudden drops in oxygen saturation are relatively common in this age group, particularly in preterm infants and after short apnoeic pauses.[7] To assess their clinical importance, reference data about patterns of oxygenation must be available. Baseline oxygenation and short lived episodes of hypoxaemia have therefore been documented from overnight 12 hour multichannel physiological recordings on a sample of 67 healthy infants in the second month of life. The relationship of these hypoxaemic episodes to breathing patterns and apnoeic pauses was determined.

Patients and methods

Using a systematic sampling procedure, 69 infants were recruited immediately after birth from all those born in one hospital who had a gestational age of at least 37 weeks and seemed healthy on medical examination in the nursery and subsequently. The study was performed at a median age of 39 days (range 29–54, interquartile range (IQR) 35–43) in the infants' homes. Recordings were made when the infants were in good health (that is, free of major symptoms from the parents' report and the researcher's observation) and not taking any drugs. Eight infants (12%) had minor problems at the time of recording (snuffly nose (n=2), thrush (n=2), colic (n=2), eye infection (n=1), and eczema (n=1)). Fully informed consent was obtained from the parents of all infants recruited.

Overnight multichannel physiological recordings started between 1830 and 2200 hours (median 2052) and lasted for a mean (SD) of 11·5 (1·1) hours. Recordings were made of arterial oxygen saturation and each photoplethysmographic pulse waveform from a pulse oximeter (Nellcor N100 with new software

Department of Paediatrics, National Heart and Lung Institute, Brompton Hospital, Dovehouse Street, London SW3 6LY
V A Stebbens
C F Poets
D P Southall

Hazleton UK Ltd
J R Alexander

Doncaster Royal Infirmary
W A Arrowsmith

Correspondence to:
Dr Southall.

Accepted 13 December 1990

equivalent to N200 and specially modified to provide beat to beat data). The oximeter sensor was taped around the lateral edge of the infant's foot. In addition, abdominal breathing movements from a volume expansion sensor (Graseby Dynamics, in 73%) or respiratory inductance plethysmography system (Studley Data Systems, in 27%) were recorded. The volume expansion capsule was taped with concentric strips of adhesive tape (3M Micropore) midway between the umbilicus and xiphisternum. Inductance plethysmography was obtained using a purpose made vest (PK Morgan).

Data were recorded onto a four channel FM tape recorder (Racal, frequency response DC to 313 Hz, signal:noise ratio 47 dB/channel) at a tape speed of 15/16 inches/second. Oxygen saturation recordings were calibrated to markers of 0, 50, and 100% generated from the oximeter. The recordings were printed onto graph paper by an ink jet recorder at 3·2 mm/second. Two recordings (3%) had poor quality oxygen saturation signals throughout and were removed from the study. Analysis of the remaining 67 recordings was done manually by two experienced workers according to the following criteria:

- *Regular and non-regular breathing patterns*—A regular breathing pattern was signified by episodes of at least one minute in duration during which the abdominal wall movement waveform was steady in rate and amplitude.[8] All periods of the recording not conforming to the above definition, or periods in which the steady pattern was disrupted by body movements, frequent sighs, or apnoeic pauses were classified as non-regular breathing patterns. Episodes of periodic apnoea were included in non-regular breathing patterns. The classification of regular breathing has previously been shown to be reproducible.[8]
- *Pauses in breathing movements*—These were classified as apnoeic if they lasted for 4 seconds or more measured from the end of the expiratory movement waveform to the onset of the inspiratory movement waveform (fig 1). Pauses were classified according to their duration (4·0–7·9, 8·0–11·9, and ≥12 seconds). Episodes in which there were three or more successive apnoeic pauses, each separated by less than 20 breaths, were classified as periodic apnoea.[8]
- *Baseline oxygen saturation and episodic desaturation*—Oxygen saturation measurements were made only after an assessment of the accompanying photoplethysmographic pulse waveforms. Any period in which the quality of this signal was unsatisfactory was excluded from the analysis (fig 1). The remaining oxygenation signal was measured in two ways. Baseline SaO_2 was calculated for each episode of regular breathing by measuring the SaO_2 values at the end inspiration for each of five successive breaths at the centre of each episode of regular breathing. These five breaths had to be at least 10 seconds away from sighs or apnoeic pauses.

During both regular and non-regular breathing patterns the duration of each episode in which SaO_2 fell to 80% or below was measured (fig 1). The minimum duration measured was 0·3 seconds. These desaturations were classified as related to apnoeic pauses if the beginning of an apnoeic pause and of a subsequent desaturation were separated by a period of 2·0–12·0 seconds. This time was defined after measurement of the total response time of the pulse oximeter in the beat to beat mode[6] and examination of pilot data.

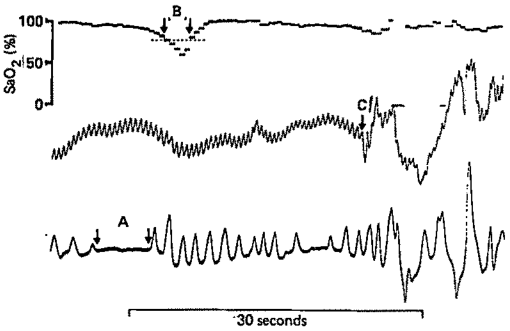


Figure 1 Section of a recording on an infant studied at the age of 35 days. The uppermost signal is oxygen saturation and the middle signal the plethysmographic pulse waveforms from which the saturation values were derived; both signals were generated from the pulse oximeter in the beat to beat mode. The lowest signal is abdominal wall breathing movements, showing a non-regular breathing pattern. At point A there is an apnoeic pause with a duration of 5·3 seconds, which is associated with a period of desaturation ≤80% lasting 2·5 seconds (B). The pulse signal can be analysed until point C, at which time body movement (note the increased volume of breathing movement) disrupts the waveform, and the subsequent saturation signal shows unreadable values.

Rates of desaturation/hour of artefact free signal and the mean durations of these episodes were calculated for each recording. The significance of the differences was assessed by the Wilcoxon signed rank test, and correlations were tested by the Spearman rank correlation coefficient. Results are expressed as median (range) for individual recordings.

Results

All measurements of oxygenation were correlated with postnatal age at the time of recording. Coefficients for these correlations were all close to zero, and there was thus no evidence that age had an influence on the results within the range studied. The data are therefore presented without reference to age.

The median duration of regular breathing pattern was 3·0 hours (range 1·1–5·8) and that of non-regular breathing pattern 8·8 hours (6·0–10·3). The median duration of artefact free SaO_2 signal was 2·9 hours (1·1–5·4) during regular breathing pattern and 4·6 hours (2·3–6·9) during non-regular breathing pattern.

During the periods in which there was an artefact free SaO_2 signal, all recordings showed apnoeic pauses, with a median value of 6·8 (0·4–72·0) pauses/hour. Thirty three infants (49%) had episodes of periodic apnoea. The median total duration of periodic apnoea in these infants was 0·3 (0·1–14·5) minutes/hour.

The median baseline SaO_2 was 99·8% (range 97·0–100%). Analysis of variability in baseline SaO_2 measurements within individual recordings showed a median SD of 0·2% (range 0–1·4%). There was therefore low variability in baseline SaO_2 among different episodes of regular breathing in the same recording.

Of 67 recordings, 54 (81%) contained episodes in which the SaO_2 fell to 80% or below, with a median of 0·9 episodes/hour (range 0–15·1) for all recordings. The median of the mean duration of these episodes for individual recordings was 1·2 seconds (0·3–2·2). The median for the longest individual desaturation in each recording was 2·4 seconds (0·3–8·6). Looking at all the desaturations, 97% lasted less than 4·0 seconds (only 24 desaturations in 11 recordings lasting for 4·0 seconds or longer).

The median number of desaturations/hour was 0·0 (0·0–1·7) during regular breathing compared with 1·5 (0–23·1) during non-regular breathing) ($p<0·001$) (fig 2). The median of the mean durations of desaturations was 0·8 seconds (0·3–1·6) during regular breathing compared with 1·1 seconds (0·3–2·9) during non-regular breathing ($p<0·05$). During regular breathing 98% of desaturations were associated with an apnoeic pause; during non-regular breathing this proportion was 65% ($p<0·01$).

The proportion of apnoeic pauses followed by a desaturation (table) varied with the duration of pause and the breathing pattern. The proportion was lowest during regular breathing (regardless of duration) and highest during periodic apnoea, particularly in association with long pauses. The differences were significant when pauses of <8·0 seconds were compared with pauses of 8·0–11·9 seconds in duration during periodic apnoea ($p<0·05$), and when isolated short pauses during regular compared with non-regular breathing were compared ($p<0·001$). Pauses of ≥12·0 seconds were so infrequent (10 in eight infants) that they did not provide adequate information for analysis in any of the breathing/pause pattern categories.

To assess whether the infants with more pauses also had a higher percentage of pauses associated with desaturation we calculated the Spearman correlation coefficient for these two variables, but it was poor (r=0·23).

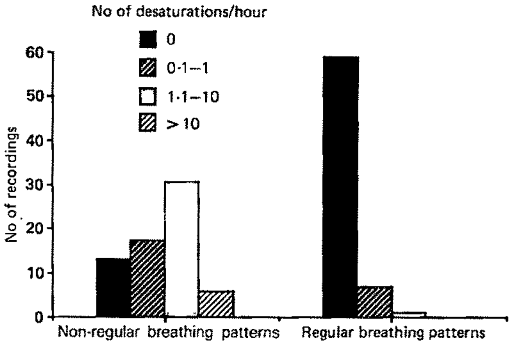


Figure 2 Numbers of recordings, subdivided into number of desaturations/hour of artefact free signals, for non-regular and regular breathing patterns.

Percentages of apnoeic pauses that were followed by desaturations. Medians (ranges) for differing pause durations during different breathing patterns. The number of recordings containing such pauses is given in parentheses below the results for each cell

Duration of apnoeic pause (seconds)	*Breathing pattern*		
	Regular	*Non-regular*	
		Isolated pauses	*Pauses in periodic apnoea*
4·0–7·9	0 (0–46) (n=64)	9·1 (0–67) (n=67)	5·9 (0–67) (n=33)
8·0–11·9	0 (0–50) (n=24)	0 (0–100) (n=34)	36·8 (0–100) (n=14)

Discussion

We have studied reference data for variables concerning breathing movements patterns and oxygenation in full term infants at about 6 weeks of age. Interestingly, there were no obvious developmental changes in oxygenation over the age range included in the study. Analysis of similar recordings in a subgroup of infants studied sequentially between the ages of 6 weeks and 1 year showed no major changes in either baseline SaO_2 or short lived falls in SaO_2 during the period analysed (unpublished data). Thus arterial oxygenation seems to be relatively stable beyond the neonatal period.

The distribution of regular and non-regular breathing patterns has been described by Richards *et al.*[8] The present results are similar to those of that study, in which 24 hour recordings of breathing movements and electrocardiograms in infants of comparable age were analysed. Assuming that a regular breathing pattern is highly correlated with a state of quiet sleep,[9] our finding of three hours of regular breathing during an overnight recording is comparable with figures given in other studies for the duration of quiet sleep in this age group.[10 11] One limitation of this method is that both awake and active sleep periods are included in non-regular breathing. Information about differences in oxygenation and respiratory patterns between these states is therefore not available from this analysis.

Comparison of the frequency of apnoeic pauses with data from other studies is difficult, because there is no common definition of apnoeic pauses.[12] Our results, however, are similar to those of Richards *et al* who included all apnoeic pauses of ≥3·6 seconds in duration.[8]

The baseline oxygen saturation measurement made during regular breathing was high in all infants, with little variability between different measurement points in the same recording. Our values are higher than those given by Mok *et al* who used the same oximeter.[13] They did not assess the quality of the photoplethysmographic waveforms, however, and so artefactually depressed values could have been incorporated in their results. In addition, their measurements were calculated as an average of all SaO_2 values occurring at a fixed sampling interval, so they potentially included desaturations in their analysis and failed to distinguish between breathing patterns.

Desaturations were present in most infants, but they were usually short, 97% being less than 4 seconds long. During regular breathing almost all desaturations followed an apnoeic pause. During non-regular breathing a third of the desaturations were not preceded by apnoeic pauses of 4·0 seconds or more in duration. Some of these latter desaturations may have reflected a response to pauses shorter than 4 seconds; others may have been accompanied by continued abdominal wall movements, with or without continued airflow.[7] Recordings that include respiratory airflow would be required to investigate these phenomena fully.

The proportion of apnoeic pauses followed by a desaturation may be an indicator of the oxygen stores in the lung, the oxygen consumption, and of the matching of ventilation to perfusion. Interestingly, less than half the recordings that showed apnoeic pauses during regular breathing showed any of these pauses followed by a desaturation to 80% or less. The proportion of short pauses associated with desaturations increased significantly during non-regular breathing. Active sleep is included in non-regular breathing, and this increase between regular and non-regular breathing patterns might, at least in part, be explained by an increase in oxygen consumption, and possibly a reduction in intrapulmonary oxygen stores, during active sleep.[14 15]

During periodic apnoea, over half of the 14 recordings showing longer pauses (8·0 to 11·9 seconds) had more than one third of such pauses followed by a desaturation. Similar findings about the effect of periodic breathing on oxygenation were reported by Mok *et al* who, by using methods that absorbed episodic desaturation values into their average values of saturation, found a mean decrease of 26% from baseline measurements during periodic breathing.[13] As only a relatively small number of infants in our study had apnoeic pauses of 8 seconds or longer, the apparently stronger influence of periodic breathing on oxygenation remains a preliminary result.

Reference data about episodes of desaturation in infants have not previously been published. In this study we used a pulse oximeter that has been validated against arterial line measurements in infants.[3] We also used the oximeter in the beat to beat mode. Most infants, despite a high baseline measurement of SaO_2, showed drops in oxygenation to levels below a threshold which has been previously defined as indicating an 'abnormal' reaction to an apnoeic pause.[16 17] Most of the recorded episodes, however, were brief (<4 seconds) and would not, therefore, have been observed using a pulse oximeter that averages SaO_2 values over several seconds. In the beat to beat mode, pulse oximeters can sense short lived falls in SaO_2 that are not seen with the averaging modes used normally.

Because the short lived falls in SaO_2 that were identified by this pulse oximeter occurred in healthy infants they must be regarded as normal. Variations in either baseline oxygenation measurements, or in the duration or frequency of episodes of desaturation beyond the range given here, however, may indicate a clinically relevant disturbance of oxygenation.

It might be argued that the short lived episodes of desaturation identified by this pulse oximeter in the beat to beat mode are artefactual, but their consistent relationship to apnoeic pauses, and previous observations that similar but more severe desaturations can occur during cyanotic episodes that have been documented as 'real' by arterial blood gas analysis,[18] suggest that they do reflect true episodes of hypoxaemia. Moreover, similar short lived desaturations have been reported by other workers, not only using pulse oximetry,[13] but also ear oximetry.

Recordings of breathing movements and electrocardiograms (pneumograms) are widely used to study respiratory physiology in infants. The frequency of apnoeic pauses and the quantity of periodic breathing have been used to indicate the need for home monitoring[20] or treatment with methylxanthines.[21] From a physiological viewpoint, however, hypoxaemia seems to be a better indicator of the adequacy of ventilation and ventilation/perfusion matching.[18] Certainly these present results indicate that any recording of breathing movements without an indicator of oxygenation will produce information that is difficult to interpret. Firstly, there was poor correlation between the frequency of apnoeic pauses and the percentage of those pauses accompanied by desaturation; secondly, about a third of the desaturation episodes were not related to apnoeic pauses; and finally, the percentage of apnoeic pauses accompanied by episodes of desaturation, particularly during periodic apnoea, varied widely among individual infants.

In conclusion, our results indicate the importance of including oxygenation in studies of respiratory physiology, whether these be on healthy subjects or patients with symptoms. Although an outlying result in either the baseline oxygen saturation value or the frequency of recurrent short lived falls in SaO_2 may be helpful in assessing the severity of illness in infants with symptoms, for instance during a respiratory tract infection, the prognostic value of outlying results in infants who are symptom free remains unknown. Further prospective studies are needed to answer this potentially important question.

We thank the workers who gave careful technical effort to the study: Mary Gray, who did the recordings, Pauline Mills and Jackie Kelly who made the measurements, and Linda Alexander and Vivienne Taylor who carried out basic analyses. Thanks also to the families in Doncaster who allowed us to use their time and homes, and made the study possible. Technical advice was given by Dr W New, and computing facilities were donated by Hewlett Packard Ltd and Ashton-Tate Ltd. Mrs Stebbens was funded by the Nuffield Foundation, Dr Poets by the Deutsche Forschungsgemeinschaft, Bonn, Germany, and Dr Southall by the National Heart and Chest Hospitals, and Nellcor Inc. The study was supported by the Foundation for the Study of Infant Death, London, and by the Cot Death Fund at Doncaster Royal Infirmary.

1 Hay WW, Brockway JM, Eyzaguirre M. Neonatal pulse oximetry: accuracy and reliability. *Pediatrics* 1989;83:717–22.
2 Boxer RA, Gottesfeld I, Sharanjeet S, Lacorte MA, Parnell AV, Walker P. Noninvasive pulse oximetry in children with cyanotic congenital heart disease. *Crit Care Med* 1987;15:1062–4.
3 Southall DP, Bignall S, Stebbens VA, Alexander JR, Rivers R, Lissauer T. Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987;62:882–8.
4 Fanconi S. Reliability of pulse oximetry in hypoxic infants. *J Pediatr* 1988;112:424–7.
5 Severinghaus JW, Naifeh KH, Koh SO. Errors in 14 pulse oximeters during profound hypoxia. *J Clin Monit* 1989;5:72–81.
6 Abraham NG, Stebbens VA, Samuels MP, Southall DP. Investigation of cyanotic/apnoeic episodes and sleep-related upper airway obstruction by long-term non-invasive bedside recordings. *Pediatr Pulmonol* 1990;8:259–62.

7 Poets CF, Stebbens VA, Samuels MP, Southall DP. Patterns of breathing during hypoxaemia in preterm infants at around term (abstract). *Early Hum Dev* 1990;**22**:107–8.

8 Richards JM, Alexander JR, Shinebourne EA, de Swiet M, Wilson AJ, Southall DP. Sequential 22-hour profiles of breathing patterns and heart rate in 110 full-term infants during their first 6 months of life. *Pediatrics* 1984;**74**: 763–77.

9 Anders T, Emde R, Parmelee A. *A manual of standardized terminology techniques and criteria for scoring of states of sleep and wakefulness in newborn infants.* Los Angeles: University of California (Los Angeles) Brain Information Service, 1971.

10 Hoppenbrouwers T, Hodgman J, Arakawa K, Sterman MB. Polysomnographic sleep and waking states are similar in subsequent siblings of SIDS and control infants during the first six months of life. *Sleep* 1989;**12**:265–76.

11 Coons S, Guilleminault C. Development of sleep-wake patterns and non-rapid eye movement sleep stages during the first six months of life in normal infants. *Pediatrics* 1982;**69**:793–8.

12 Flores-Guevara R, Sternberg B, Peirano P, Guidasci N, Durupt N, Monod N. Respiratory pauses and periodic breathing assessed by cardiopneumography in normal infants and in SIDS siblings. *Neuropediatrics* 1986;**17**: 59–62.

13 Mok JYQ, McLaughlin FJ, Pintar M, Hak H, Amaro-Galvez R, Levison H. Transcutaneous monitoring of oxygenation: what is normal? *J Pediatr* 1986;**108**:365–71.

14 Stothers JK, Warner RM. Oxygen consumption and neonatal sleep states. *J Physiol (Lond)* 1978;**278**:435–40.

15 Henderson-Smart DJ, Read DJC. Reduced lung volume during behavioral active sleep in the newborn. *J Appl Physiol* 1979;**46**:1081–5.

16 Coleman JM, Mammel MC, Bing DR, Hagen EA, Boros SJ. Two vs. four channel pneumograms: the issue of SaO_2 monitoring. *Pediatr Res* 1989;**25**:305A.

17 Muttitt SC, Finer NN, Tierney AJ, Rossmann J. Neonatal apnea: diagnosis by nurse versus computer. *Pediatrics* 1988; **82**:713–20.

18 Southall DP, Samuels MP, Talbert DG. Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death. *Arch Dis Child* 1990;**65**:953–61.

19 Henderson-Smart DJ. Vulnerability to hypoxemia in the newborn. *Sleep* 1980;**3**:331–42.

20 Kelly DH, Shannon DC, O'Connell KC. Care of infants with near miss sudden infant death syndrome. *Pediatrics* 1978; **61**:511–14.

21 Hunt CE, Brouillette RT, Hanson D. Theophylline improves pneumogram abnormalities in infants at risk for sudden infant death syndrome. *J Pediatr* 1983;**103**:969–74.

Archives of Disease in Childhood 1991; **66:** 574–578

Oxygen saturation and breathing patterns in infancy.
2: Preterm infants at discharge from special care

C F Poets, V A Stebbens, J R Alexander, W A Arrowsmith, S A W Salfield, D P Southall

Abstract

Overnight 12 hour tape recordings of arterial oxygen saturation (SaO_2, pulse oximeter in the beat to beat mode), breathing movements, and airflow were made on 66 preterm infants (median gestational age 34 weeks, range 25–36) who had reached term (37 weeks) and were ready for discharge from the special care baby unit. No infant was given additional inspired oxygen during the study. The median baseline SaO_2 was 99·4% (range 88·9–100%). Eight infants had baseline SaO_2 values below 97%, the lowest value observed in a study on full term infants. All but one infant had short-lived falls in SaO_2 to ≤80% (desaturations), which were more frequent (5·4 compared with 0·9/hour) and longer (mean duration 1·5 compared with 1·2 seconds) than in full term infants. There was no evidence that gestational age at birth influenced the frequency or duration of desaturations among the preterm infants. The frequency of relatively prolonged episodes of desaturation (SaO_2 ≤80% for ≥4 seconds), however, decreased significantly with increasing gestational age (0·5, 0·4, 0·2, and 0·1 episodes/hour in infants at ≤32, 33–34, 35, and 36 weeks' gestational age, respectively). Analysis of the respiratory patterns associated with such episodes showed that 5% occurred despite both continued breathing movements and continuous airflow. Five infants had outlying recordings: three had baseline SaO_2 values of less than 95% (88·9, 92·7, and 93·8%), and two had many prolonged desaturations (14 and 92/hour; median for total group 0·2, 95th centile 2·3). None of these five infants had been considered clinically to have a disorder of oxygenation.

Although these data are insufficient to provide information about outcome, we conclude that reference data on arterial oxygenation in preterm infants are important to enable the identification of otherwise unrecognised hypoxaemia.

Department of Paediatrics, National Heart and Lung Institute, Brompton Hospital, Dovehouse Street, London SW3 6LY
C F Poets
V A Stebbens
D P Southall

Hazleton UK Ltd
J R Alexander

Doncaster Royal Infirmary
W A Arrowsmith

Rotherham District General Hospital
S A W Salfield

Correspondence to:
Dr Southall.

Accepted 13 December 1990

Preterm infants have significantly more apnoeic pauses and periodic breathing when they reach term than infants who are born at term,[1] particularly if they have a previous history of apnoea of prematurity.[2] Apnoeic pauses may be triggered by chronic hypoxaemia,[3] or may themselves cause episodic hypoxaemia. Short lived falls in oxygen saturation seem to be normal among infants.[4 5] If we want to identify abnormal hypoxaemia, therefore, we need to know about normal variability in arterial oxygenation in this particular group of infants.

Currently, there is little knowledge about normal arterial oxygenation in infancy. In a previous study we analysed arterial oxygen saturation and breathing movements in healthy full term infants in their second month of life.[4] In the present study, the same techniques have been applied to a group of preterm infants who were studied when they were ready for discharge from the special care baby unit and had reached at least 37 weeks' gestation. Two specific questions were asked: what is the influence of gestational age on the pattern of oxygenation, and (based on our study of term infants[4]) how does oxygenation differ between full term and preterm infants?

Patients and methods

Between August 1986 and July 1987 all preterm infants who were born at three maternity hospitals and who received special care immediately after birth had overnight tape recordings made of selected physiological variables. The study was carried out when infants were assessed as ready for discharge, and only on those who were considered to have a good prognosis for survival. A total of 305 infants fulfilled the criteria, and 261 (86%) had parental consent for the investigation. The project was approved by the hospitals' ethics committees. For the purpose of this study, all 72 infants with gestational ages of 37 weeks or more at the time of discharge, and who underwent their recordings within the three days before discharge, were included in the analysis.

All 72 infants underwent 12 hour overnight recordings of arterial oxygen saturation (SaO_2) (Nellcor N100 with new software equivalent to N200 and specially modified to provide beat to beat data); each photoplethysmographic pulse waveform from a pulse oximeter (for the validation of the saturation signals); breathing movements from a volume expansion capsule (Graseby) or from respiratory inductance plethysmography (Studley Data Systems); and nasal airflow either through a thermistor (Yellow Springs Instruments) or from expired carbon dioxide sampling (Engström Eliza). The recordings were stored on tape (Racal FM4) and subsequently printed onto graph paper by an ink jet recorder at 3·2 mm/second. As the study was prospective and non-invasive the recordings were not used for clinical management.

Six recordings (8%) gave poor quality oxygen saturation signals throughout and were removed from the study. Of the remaining 66 recordings, 31 (47%) were done on the last day before discharge, 26 (39%) two days, and eight (12%)

three days before discharge. Eight infants were receiving drug treatment at the time of the study: antibiotics (n=6), diuretics (n=1), and theophylline (n=1). No infant was receiving additional inspired oxygen.

The recordings were analysed by two experienced workers without knowledge of the clinical history of the infants as described previously.[4] In summary, the duration of artefact free SaO_2 signal was measured. Periods of regular and non-regular breathing patterns were identified. The numbers of apnoeic pauses of 4 seconds or longer were counted. Episodes with three or more successive apnoeic pauses, each separated by less than 20 breaths, were classified as periodic apnoea.

Baseline oxygen saturation values were calculated for each episode of regular breathing by measuring the oxygen values at end inspiration for each of five successive breaths half way through the episode. In both breathing patterns the number of episodes in which SaO_2 fell to $\leqslant$80% was counted, and the time that it remained $\leqslant$80% was measured during each episode. These episodes of desaturation were classified according to their relationship with an apnoeic pause. An association with an apnoeic pause was considered to be present if the desaturation began within 2–12 seconds of the onset of the apnoeic pause.

Prolonged desaturations ($SaO_2 \leqslant 80\%$ for $\geqslant 4$ seconds) were analysed separately; in full term infants 97% of all desaturations were shorter than 4 seconds.[4] The breathing signals during each prolonged desaturation were analysed and classified according to the presence of: a pause in breathing movements; a pause in airflow only (minimum duration 4 seconds); a mixed pause with a combination of the first two; and continuous airflow with no pause in either breathing movements or airflow. If the desaturation occurred during a period in which the breathing signal was of poor quality the episode was classified as uninterpretable.

Clinical data were abstracted from the discharge summaries. Data concerning the infants' survival were collected from the National Health Service Register at the Office of Population Censuses and Surveys. Two infants died, both in the first year of life. One had a ventricular septal defect, and died at 5 months of age in the perioperative period after cardiac surgery, and one (who had developed asthma) died at 11 months in status asthmaticus. There was no death from the sudden infant death syndrome among the infants in this study.

To analyse the influence of gestational age at birth, results are presented for the total group of 66 infants and also divided into four subgroups, categorised arbitrarily before the results were examined, by gestational age (weeks) at birth: group A, $\leqslant$32 (n=16); group B, 33–34 (n=18); group C, 35 (n=16); and group D, 36 (n=16).

Rates of occurrence of desaturations/hour of artefact free signal, and their mean durations, were calculated for each recording. The significance of differences was assessed using the Kruskal-Wallis test for the comparison between the subgroups of preterm infants with different gestational ages, the Wilcoxon rank sum test and Fisher's exact test for comparisons between preterm and full term infants, and the Wilcoxon matched pairs signed ranks test for comparisons between breathing patterns. Findings are given as the median (and range of individual mean values) for each variable.

Results

Table 1 shows that the infants in the four subgroups had different postnatal, but similar postconceptional, ages at the time of the study. A history of respiratory distress or apnoea of prematurity was more common among the infants who were less mature (table 2). Two infants had congenital heart disease: one had an aortopulmonary window, and one had a ventricular septal defect. Neither had outlying results for any of the variables studied.

The median duration of artefact free signal was 2·0 hours (range 0·7–5·5) during regular breathing and 6·1 hours (2·7–8·4) during non-regular breathing. These durations were similar in all subgroups (data not shown).

During regular breathing the median number of apnoeic pauses/hour was 5·8 (0·0–19·0), with two infants having no pauses during this pat-

Table 1 Clinical data of the infants studied, according to gestational age at birth. Figures are expressed as median (range) except where otherwise stated

	Group				*Total (n=66)*
	A (n=16)	*B (n=18)*	*C (n=16)*	*D (n=16)*	
Gestational age at birth (weeks)	29 (25–32)	33·5 (33–34)	35 (35)	36 (36)	34 (25–36)
Male:female ratio	4:12	12:6	9:7	10:6	35:31
Birth weight (g)	1115 (700–1575)	1720 (1200–2280)	2030 (1410–3260)	2140 (1375–2975)	1822 (700–3260)
Postnatal age at recording (days)	78 (32–106)	26 (18–52)	15 (11–44)	15 (5–65)	24 (5–106)
Postconceptional age at recording (weeks)	39 (37–43)	37·5 (37–41)	37 (37–42)	39 (37–46)	38 (37–46)

Table 2 Clinical histories of infants according to gestational age

	Group				*Total (n=66)*
	A (n=16)	*B (n=18)*	*C (n=16)*	*D (n=16)*	
Gestational age at birth (weeks)	$\leqslant$32	33–34	35	36	25–36
Product of multiple pregnancy	4	2	2	2	10
Respiratory distress syndrome	13	9	8	5	35
Positive pressure ventilation	13	7	1	0	21
History of apnoea of prematurity	11	5	1	0	17

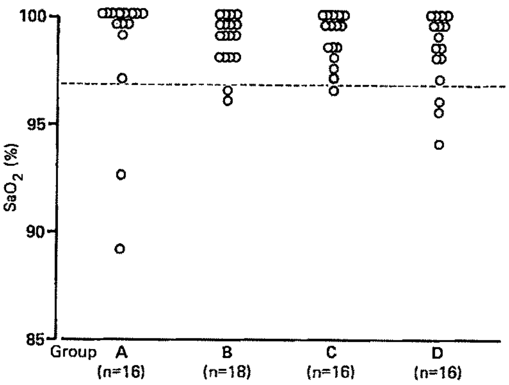


Figure 1 Distribution of baseline measurements of SaO_2 in groups of different gestational ages (weeks) at birth: group A, ≤32; B, 33–34; C, 35; and D, 36. Dotted line represents the lowest value recorded in 67 full term infants (97%).

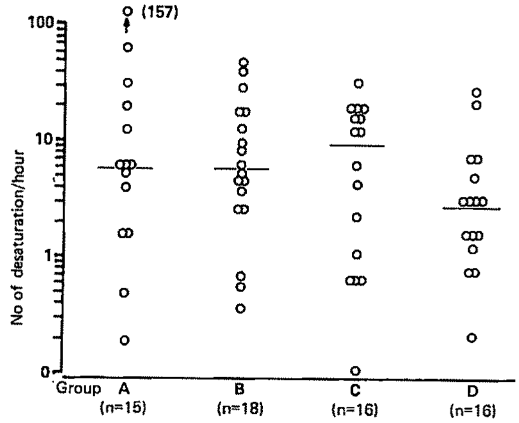


Figure 2 Distribution of desaturations (SaO_2 ≤80%/hour) in groups of different gestational ages (weeks) at birth: group A, ≤32; B, 33–34; C, 35; and D, 36. Note logarithmic scale on the y axis. Horizontal bars indicate median in each group. Values for desaturations could not be obtained for one infant in group A.

tern. All infants had pauses during non-regular breathing, with a median of 30·8 (0·5–155·2) pauses/hour. Periodic apnoea occurred in 63 (95%) infants, with a median of 14·0 (0·0–144·0) pauses/hour in this pattern. Again, values were similar in the groups with different gestational ages at birth (data not shown).

The median baseline SaO_2 was 99·4% (88·9–100). The fifth centile was 94·3%. Analysis of variability in baseline SaO_2 measurements within individual recordings showed a median SD of 0·8% (range 0–3·2%). The average variability within baseline SaO_2 measurements between different episodes of regular breathing in the same recording was thus four times higher than in the full term infants studied previously.[4]

Eight infants had a baseline SaO_2 value below 97%, the lowest level observed in normal full term infants (fig 1).[4] None of the three infants who had values below the fifth centile had been considered clinically hypoxaemic: the first, with a baseline SaO_2 of 93·8%, had never received additional inspired oxygen. The second, with a baseline of 92·7%, had been oxygen dependent until 72 days of age, but was not thought clinically to require it at the time of discharge. The infant with the lowest baseline SaO_2 (88·9%) had a gestational age of 31 weeks and had been ventilated for three days because of mild respiratory distress syndrome. She had no history of apnoea of prematurity and was clinically well. Because her SaO_2 was below 80% during a substantial part of the recording, it was excluded from further analysis of episodic desaturation below 80%.

All but one recording contained episodes during which SaO_2 fell transiently to 80% or less (table 3). The frequency and mean duration of these desaturations were similar in the groups with different gestational age (table 3, fig 2). The duration of the longest desaturation observed in each recording, as well as the proportion of apnoeic pauses that was followed by a desaturation, decreased with increasing gestational age, but the differences between the groups were not significant (table 3). There were, however, significant differences for all variables between different breathing patterns: desaturations were more frequent and were longer during non-regular than during regular breathing, and the proportion of apnoeic pauses followed by a desaturation was also higher during non-regular breathing (table 3). All variables differed significantly from those previously obtained in full term infants (table 4).

Analysis of prolonged desaturations (SaO_2 ≤80% for ≥4 seconds) showed that 44 infants (68%) had a total of 822 such episodes, with a median frequency of 0·2 (0·0–92·4) per hour (fig 3). This frequency decreased significantly with increasing gestational age ($p<0·02$). The analysis of the associated breathing pattern showed that most of the prolonged desaturations (534 (65%) in 28 infants) followed pauses during periodic apnoea; and 144 (18%) in 31 infants followed isolated apnoeic pauses, almost all of these occurring during non-regular breathing.

*Table 3 Results of arterial oxygen saturation measurements. Values are expressed as median (range) except where otherwise stated; *$p<0·05$, **$p<0·01$, *** $p<0·001$, regular compared with non-regular breathing patterns*

	Breathing pattern	*Group*				*Total (n=65)*
		A (n=15)	*B (n=18)*	*C (n=16)*	*D (n=16)*	
Gestational age at birth (weeks)		≤32	33–34	35	36	25–36
No of desaturations (SaO_2≤80%)/hour	Regular	0·4 (0·0–40·1)***	0·0 (0·0–12·0)***	0·0 (0·0–2·7)***	0·0 (0·0–4·9)***	0·0 (0·0–40·1)***
	Non-regular	7·6 (0·2–164·9)	8·8 (0·3–63·4)	12·0 (0·0–41·7)	3·9 (0·0–29·5)	7·2 (0·0–164·9)
Mean duration of desaturations (seconds)	Regular	0·9 (0·3–3·2) (n=8)**	1·1 (0·3–2·7) (n=7)*	1.9 (0·6–2·0) (n=7)	0·9 (0·3–1·2) (n=5)	1·1 (0·3–3·2) (n=27)***
	Non-regular	1·7 (0·7–4·4) (n=15)	1·6 (0·5–3·3) (n=18)	1.6 (0·6–3·3) (n=15)	1·3 (0·6–2·4) (n=15)	1·5 (0·5–4·4) (n=63)
Duration of longest desaturation (seconds)	Regular+ non-regular	7·2 (1·1–26·9)	7·7 (0·8–26·9)	5·0 (0·3–13·8)	3·9 (0·3–17·0)	5·1 (0·3–26·9)
No of desaturations ≥4 seconds/hour	Regular+ non-regular	0·5 (0·0–92·4)	0·4 (0·0–14·2)	0·2 (0·0–2·3)	0·1 (0·0–0·4)	0·2 (0·0–92·4)
Percentage of apnoeic pauses that were followed by a desaturation	Regular	2 (0–100)	0 (0–64)***	0 (0–33)**	0 (0–86)**	0 (0–100)***
	Non-regular	12 (0–96)	18 (0–70)	11 (0–43)	6 (0–58)	12 (0–96)***

Table 4 Comparison of results between full term and preterm infants. Figures are expressed as median (range) except where otherwise indicated. Values for desaturations could not be obtained in one preterm infant.

	Full term infants (n=67)	*Preterm infants (n=66)*	*p Value*
Age at recording (days)	39 (29–54)	23 (5–106)	Not applicable
No of apnoeic pauses/hour	6·8 (0·4–72·0)	25 (1·0–147·3)	<0·0001
No (%) infants with periodic apnoea	33 (49·3)	63 (94)	<0·0001
Baseline SaO_2 measurement (%)	99·8 (97·0–100)	99·4 (88·9–100)	<0·01
No (%) infants with $SaO_2 \leqslant 80\%$	54/67 (81)	64/65 (99)	<0·02
No of desaturations/hour	0·9 (0·0–15·1)	5·4 (0·0–156·5)	<0·0001
Mean duration of desaturation (seconds)	1·2 (0·3–2·2)	1·5 (0·3–4·4)	<0·001
Duration of longest desaturation (seconds)	2·4 (0·3–8·6)	5·1 (0·0–26·9)	<0·0001

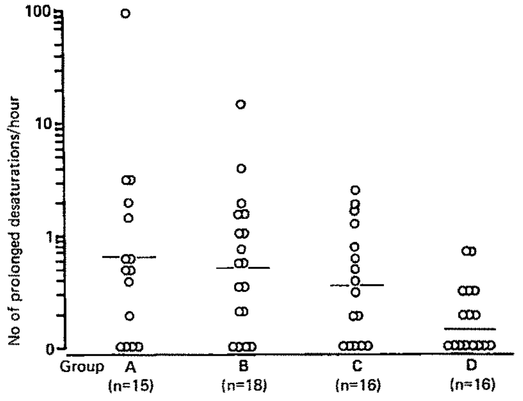


Figure 3 Distribution of prolonged desaturations (SaO_2 $\leqslant 80\%$ for $\geqslant 4$ seconds/hour) in groups of different gestational ages (weeks) at birth: group A, $\leqslant 32$; B, 33–34; C, 35; and D, 36. Note logarithmic scale on the y axis. Horizontal bars indicate median in each group. Values for desaturations could not be obtained for one infant in group A.

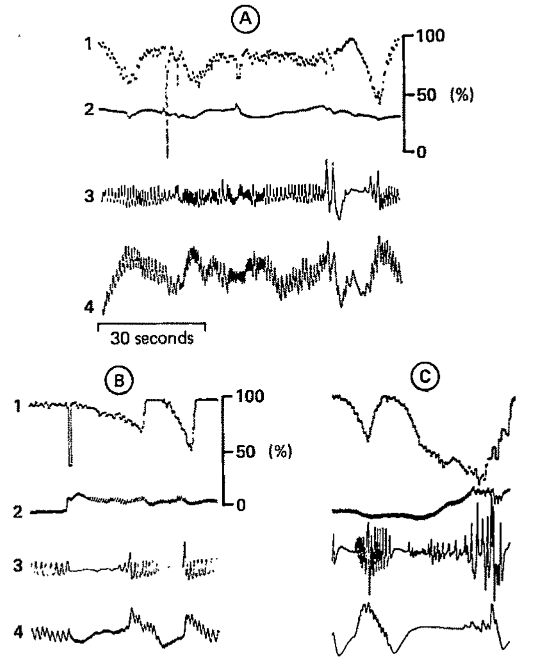


Figure 4 Examples of the different breathing patterns during prolonged desaturations: 1=arterial oxygen saturation; 2=photoplethysmographic waveform; 3=breathing movements (pressure capsule); and 4=nasal airflow (thermistor). (A) shows two episodes of desaturation despite continued breathing movements and airflow, followed by a desaturation associated with a short apnoeic pause. The shape of the saturation signal is similar during both patterns. (B) shows two pauses in breathing movements and airflow of 15 and 7 seconds duration, respectively. (C) shows a mixed pause (21 seconds) with a pause in breathing movements and airflow that is followed by cessation of airflow only.

Forty one (5%) were associated with an absence of airflow, 12 of these being mixed pauses. Thirty seven prolonged desaturations (5%) in 17 infants occurred despite the continuation of both breathing movements and airflow. In the remaining 7% airflow signals were uninterpretable. Examples of the different breathing patterns during prolonged desaturations are shown in fig 4.

There were two infants who had values far outside the range of all other infants (fig 3). One infant, who had a total of 104 prolonged desaturations (14·2/hour), had a gestational age of 34 weeks and had had recurrent apneoa and bradycardia that were reported to have ceased a week before discharge. Her baseline SaO_2 was 98·9% The other infant, who had a total of 382 prolonged desaturations (92·4/hour), 362 of them during periodic apnoea, was born at 26 weeks' gestation (birth weight 775 g), and had had positive pressure ventilation for the first four weeks of life. Her baseline SaO_2 was 97·1%. She was also the infant with the highest number of short desaturations, and the only infant in whom more than 95% of apnoeic pauses were followed by a desaturation during both regular and non-regular breathing patterns. Both infants were clinically well at the time of the recordings.

Discussion

The present study, in which we used a pulse oximeter in the beat to beat mode that has been validated against arterial line measurements,[6 7] provides the first reference data for SaO_2 in preterm infants. The infants studied were a heterogeneous group covering a wide range of gestational ages at birth, and different medical histories, because we wanted to provide representative data for preterm infants leaving special care. We were therefore careful not to apply too restrictive entry criteria for the infants that were enrolled in this study. So that the data could be compared, however, it was necessary to include only infants who had reached term at the time of their discharge.

There were relatively small differences in the number and duration of desaturations between subgroups with different gestational ages at birth but similar postconceptional ages at the time of study. This finding is in agreement with that of Hinkes on breathing movements in preterm infants; he also showed a wide scattering in the number of apnoeic pauses in infants with different gestational ages.[8] Our data, however, show that the frequency of prolonged desaturations increased with decreasing gestational age at birth (fig 3). This, and the fact that there were highly significant differences for all variables between these preterm infants and the full term infants (table 4), suggest that gestational age at birth may have some influence on the development of stability in arterial oxygenation.[4] This influence, however, is overlaid by the large interindividual variability in the frequency of desaturations in this group of infants. The comparison with full term infants is additionally compromised by the fact that the full term infants were older at the time of study and had a narrower age range, specifically omitting the neonatal period. The indications that maturity at birth is an independent factor for the developmental of stability in oxygenation cannot therefore be confirmed by these data. Further studies of larger numbers of infants are necessary to answer this question.

Interestingly, with few exceptions, the preterm infants had baseline values of SaO_2 in the same range at the full term infants.[4] This means that during stable conditions most preterm infants had normal SaO_2 The variability in baseline SaO_2 in the same recording, however, was considerable. This suggests that making only one measurement during quiet sleep may not provide reliable information about baseline SaO_2 in infants born before full term.

The present data clearly show the influence of breathing pattern on arterial oxygenation. During regular breathing, which is highly correlated with the state of quiet sleep,[9] most of the infants did not have any episodes of desaturation, and when episodes did occur, they were usually short (in 95% of infants the longest desaturation during regular breathing was less than 4 seconds long). The opposite was true during non-regular breathing; apnoeic pauses occurring during non-regular breathing are more likely to be associated with a desaturation.[4] Non-regular breathing includes active sleep, and possible reasons for an increase in the frequency of desaturations include increased oxygen consumption and reduced intrapulmonary oxygen stores.[10] [11] In preterm infants, who have lower functional residual capacity and more compliant chest walls, the influence of active sleep may be even more pronounced.[12]

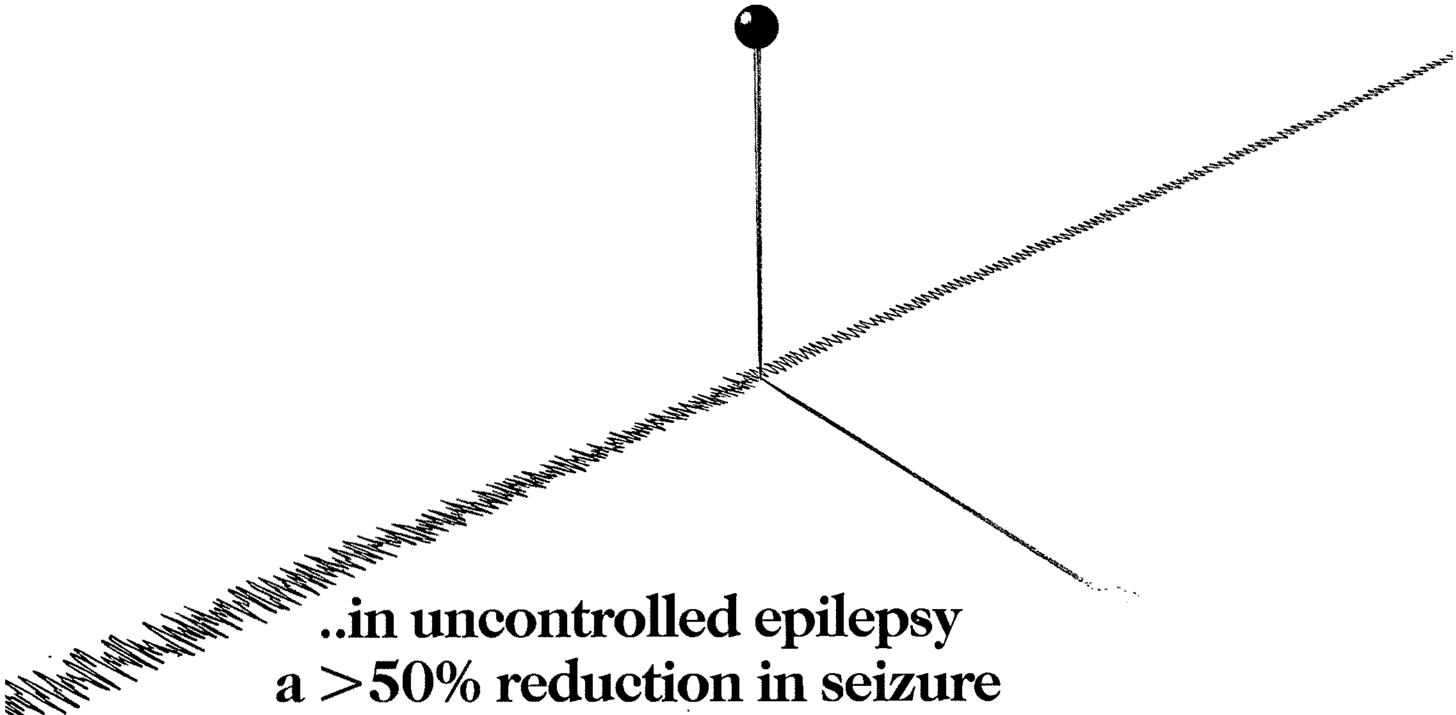
In a previous study we described the occurrence of intermittent arterial hypoxaemia despite continued breathing movements and nasal airflow.[5] This was most common in preterm infants being investigated for cyanotic episodes, but also in two of 16 preterm controls who had no symptoms. None of these infants (cases or controls) had a structural congenital heart lesion that could have produced a right to left shunt and resultant ventilation/perfusion mismatch. An intermittent intrapulmonary right to left shunt was, therefore, considered to be the most likely cause of these hypoxaemic episodes.[5] [13] The analysis of breathing patterns during prolonged desaturations performed in the present study confirms our previous observation that the potential to develop a mismatch between ventilation and perfusion may also be present in clinically well preterm infants.

The large interindividual variability in the frequency of short lived desaturations reduces their usefulness as markers of abnormal respiratory pathophysiology. The frequency of prolonged desaturations, and the baseline SaO_2 values, however, showed less variability between subjects and may therefore serve as indicators for hypoxaemia. Using these variables, five infants in this study were identified as clear outliers at the time of their discharge from hospital: three with baseline SaO_2 values below 95% (one only 89%) and two with large numbers of prolonged desaturations. Our sample is not large enough to provide information about the outcome of these infants. There is evidence, however, that chronic or acute intermittent hypoxaemia may be a contributing factor to sudden infant death,[13–15] and that chronic hypoxaemia may reduce the amount of weight gained by preterm infants.[16] This condition should therefore be identified and treated. Further prospective studies on the reproducibility and prognostic significance of outlying results should be done, however, before similar long term recordings of arterial oxygen saturation and breathing patterns can be advocated for all preterm infants before discharge from special care baby units.

We thank the workers who gave careful technical effort to the study: Mary Gray, Gill Crowther, Jean Tait, Barbara Neville, and Pat Allison who took the recordings, Pauline Mills and Jackie Kelly who made the measurements, and Linda Alexander and Vivienne Taylor who carried out basic analyses. Thanks also to the medical, nursing, secretarial, and medical records staff at Doncaster Royal Infirmary and Rotherham and Barnsley District General Hospitals. Particular thanks to Dr Bridson and the families of the babies being given special care at these hospitals. Technical advice was given by Dr W New, and computing facilities were donated by Hewlett Packard Ltd and Ashton-Tate Ltd. Dr Poets was funded by the Deutsche Forschungsgemeinschaft, Bonn, Germany, Mrs Stebbens by the Nuffield Foundation, and Dr Southall by the National Heart and Chest Hospitals, and Nellcor Inc. The study was supported by the Cot Death Fund at Doncaster Royal Infirmary.

1 Albani M, Bentele KHP, Budde C, Schulte FJ. Infant sleep apnea profile: preterm vs. term infants. *Eur J Pediatr* 1985; **143**:261–8.
2 Hageman JR, Holmes D, Suchy S, Hunt CE. Respiratory pattern at hospital discharge in asymptomatic preterm infants. *Pediatr Pulmonol* 1988;**4**:78–83.
3 Rigatto H, Brady JB. Periodic breathing and apnea in preterm infants. II. Hypoxia as a primary event. *Pediatrics* 1972;**50**:219–27.
4 Stebbens VA, Poets CF, Alexander JA, Arrowsmith WA, Southall DP. Oxygen saturation and breathing patterns in infancy. 1: Full term infants in the second month of life. *Arch Dis Child* 1991;**66**:569–73.
5 Poets CF, Stebbens VA, Samuels MP, Southall DP. Patterns of breathing during hypoxaemia in preterm infants at around term (abstract). *Early Hum Dev* 1990;**22**:107–8.
6 Fanconi S, Doherty P, Edmonds JF, Barker GA, Bohn DJ. Pulse oximetry in pediatric intensive care: comparison with measured saturations and transcutaneous oxygen tension. *J Pediatr* 1985;**107**:362–6.
7 Southall DP, Bignall S, Stebbens VA, Alexander JR, Rivers RPA, Lissauer T. Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987;**62**:882–8.
8 Hinkes P. Persistent apnea and bradycardia of prematurity. *Perinatol Neonatol* 1984;**8**:17–25.
9 Anders T, Emde R, Parmelee A. *A manual of standardized terminology techniques and criteria for scoring of states of sleep and wakefulness in newborn infants*. Los Angeles: University of California (Los Angeles) Brain Informatin Service, 1971.
10 Stothers JK, Warner RM. Oxygen consumption and neonatal sleep states. *J Physiol (Lond)* 1978;**278**:435–40.
11 Henderson-Smart DJ, Read DJC. Reduced lung volume during behavioral active sleep in newborn. *J Appl Physiol* 1979;**46**:1081–5.
12 Stark AR, Cohlan BA, Waggener TB, Frantz ID III, Kosch PC. Regulation of end-expiratory lung volume during sleep in premature infants. *J Appl Physiol* 1987;**62**:1117–23.
13 Southall DP, Samuels MP, Talbert DG. Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death. *Arch Dis Child* 1990;**65**:953–61.
14 Guntheroth WG, Kawabori I, Breazeale DG, Garlinghouse LE, van Hoosier GL. The role of respiratory infection in intrathoracic petechiae. *Am J Dis Child* 1980;**134**:364–6.
15 Rognum TO, Saugstad OD, Øyasoeter S, Olaisen B. Elevated levels of hypoxanthine in vitreous humour indicate prolonged cerebral hypoxia in victims of sudden infant death syndrome. *Pediatrics* 1988;**82**:615–8.
16 Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. *Am J Dis Child* 1987;**141**:992–5.

A breakthrough in seizure control...



..in uncontrolled epilepsy a >50% reduction in seizure frequency in approximately 50% of patients(1)

- No therapeutically significant drug interactions with other anti-convulsants(2-5)*
- Flexible dosing - once or twice daily

▼ SABRIL®

VIGABATRIN

Specific GABA-transaminase inhibition for uncontrolled epilepsy

Decreases of about 20% in plasma phenytoin levels have been reported but these are unlikely to be of therapeutic significance.

MERRELL DOW

Merrell Dow Pharmaceuticals Limited, Lakeside House, Stockley Park, Uxbridge, Middlesex UB11 1BE

TRADEMARKS Sabril, Merrell Dow.

Abridged Prescribing Information and references appear on the following page.

SAB 5 90

Abridged Prescribing Information
SABRIL Tablets ▼

Presentation: White tablets with a breakline marked SABRIL, each containing 500mg vigabatrin.
Uses:
Indications: Treatment of epilepsy not controlled by other antiepileptic drugs.
Dosage and Administration: Oral administration once or twice daily added to the patient's current therapeutic regimen.
Adults: Recommended starting dose 2g/day. Increased or decreased in 0.5g or 1.0g increments depending upon clinical response and tolerability. Maximum 4g/day. There is no direct correlation between plasma concentration and efficacy.
Children: Recommended starting dose 1g/day in ages 3-9 years and 2g/day if older.
Elderly: Consider dose reduction in patients with impaired renal function.
Contra-indications, Precautions, Warnings etc.:
Use in pregnancy and lactation: Contra-indicated.
Precautions: Abrupt withdrawal may lead to rebound seizures. Caution in patients with history of psychosis or behavioural problems. Caution in elderly patients, particularly creatinine clearance below 60ml/min. Reduce dose and monitor closely for adverse events.
Warnings: Vigabatrin causes intramyelinic oedema in the brain white matter tracts of animals but there is no evidence of this in man. However, monitor patients for neurological changes. See the full product data sheet.
Effects on driving ability: Drowsiness has been seen and patients should be warned.
Side-effects: Are mainly CNS related. Aggression and psychosis have been reported and a previous history of psychosis or a behavioural problem appears to be a predisposing factor. Other reported events: drowsiness and fatigue, dizziness, nervousness, irritability, depression, headache and less commonly confusion, memory disturbance and vision complaints; also weight gain and minor gastrointestinal side-effects. Also in children excitation and agitation. Some patients may experience an increase in seizure frequency with vigabatrin, particularly those with myoclonic seizures. Tests have not revealed evidence of neurotoxicity in humans. Lab data do not indicate renal or hepatic toxicity. Decreases in SGOT and SGPT have been observed. Chronic treatment may lead to a slight decrease in haemoglobin.
Drug Interactions: are unlikely. A gradual reduction of about 20% in plasma phenytoin concentration has been observed. No clinically significant interactions with carbamazepine, phenobarbitone or sodium valproate.
Legal Category: POM
Package Quantities: Blister strips of 10 in cartons of 100.
Product Licence Number: PL 4425/0098.
NHS Price: Pack of 100 tablets: £46.
Date of Preparation: December 1990
You must refer to the full prescribing information before administering Sabril. Further information including full product data sheet is available from the Licence Holder:
Merrell Dow Pharmaceuticals Ltd, Lakeside House, Stockley Park, Uxbridge, Middlesex UB11 1BE.

References
1. Mumford JP. Br J Clin Pract 1988; 42 (Suppl 61): 7-9. 2. Browne TR, *et al.* Neurology 1987; 37: 184-189. 3. Tartara A, *et al.* Epilepsia 1986; 27: 717-723. 4. Tassinari CA, *et al.* Arch Neurol 1987; 44: 907-910. 5. Rimmer EM, Richens A. Lancet 1984; 1: 189-190.

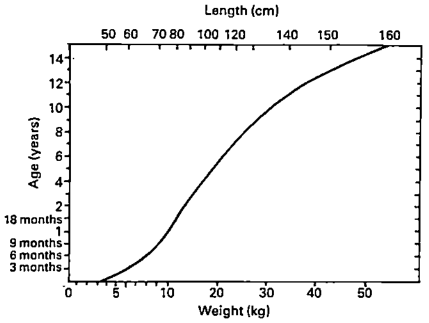
Trademarks: Sabril, Merrell Dow.

MERRELL DOW

Endotracheal tube

Length (cm)	Internal diameter (mm)
18–21	7·5–8·0
18	7·0
17	6·5
16	6·0
15	5·5
14	5·0
13	4·5
12	4·0
	3·5
10	3·0–3·5

Paediatric resuscitation chart



Adrenaline (ml of 1/10 000) intravenous or endotracheal	0·5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal	0·1	0·2	0·4	0·6	0·6	0·6
Bicarbonate (ml of 8·4%) intravenous	5	10	20	30	40	50
Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
Diazepam (mg) intravenous	1·25	2·5	5	7·5	10	10
per rectum	2·5	5	10	—	—	—
Glucose (ml of 50%) intravenous	10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal	5	10	20	30	40	50
Salbutamol (µg) intravenous	25	50	100	150	200	250
Initial DC defibrillation (J)	10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)	50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml ≡ 1·5 ml calcium chloride 10% ≡ 4·5 ml calcium gluconate 10%

A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

Poster: UK £3.50; Abroad £4.50 including packing and postage, by air abroad.
Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.
Credit cards are accepted: ACCESS, VISA, AMERICAN EXPRESS (please give full details)

BMJ BRITISH MEDICAL JOURNAL, BMA HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR

Archives of Disease in Childhood 1991; **66:** 579–583

GP 24944

Airway response to exercise and methacholine in children with respiratory symptoms

J B Clough, S A Hutchinson, J D Williams, S T Holgate

University of Southampton Department of Immunopharmacology, Medicine 1, Level D, Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY
J B Clough
S T Holgate

Medical School
S A Hutchinson

Department of Medical Statistics and Computing
J D Williams

Correspondence to:
Professor Holgate.

Accepted 3 December 1990

Abstract

Thirty atopic and 30 non-atopic subjects were identified from a population of 7–8 year old children with current respiratory symptoms. The response of the airways to exercise and provocation by methacholine were compared. In these children, who had symptoms but were not necessarily asthmatic, there was no significant correlation between the two stimuli. The atopic children were, however, significantly more responsive than the non-atopic children to both. For the whole group, odds ratios derived for atopy and for an increased response to methacholine (expressed as a PD$_{20}$—the dose that caused the forced expiratory volume in one second (FEV$_1$) to fall by 20%—of $<6{\cdot}4$ µmol/l), a positive exercise test ($>15\%$ fall in FEV$_1$), and the presence of asthma were 13·5, 3·3, and 21·0, respectively; that for positive response to methacholine and positive exercise challenge was 1·5. Thus though increased bronchial responsiveness to methacholine and exercise challenge are both associated with a diagnosis of asthma, the association between the two stimuli is complex, and supports the view that they reflect entirely different components of airways dysfunction.

There is no universally accepted definition of asthma, although it is usually described clinically as reversible airways obstruction. Increasingly the word 'asthma' is used to embrace a range of diseases with the common end points of increased airways resistance and increased bronchial responsiveness. Establishing a diagnosis of asthma purely on clinical grounds can be difficult. There are no symptoms that are specific for asthma, especially in childhood when recurrent cough—particularly at night—is common. Attempts to delineate symptom complexes that are more specific for 'asthma' than single symptoms have not been successful.[1] The recognition that enhanced responsiveness of the airways to various diff-erent stimuli often accompanied established asthma raised the possibility that a formal assessment of this component of airways dysfunction by provocation testing might provide the objective measurement that would enable the diagnosis of asthma to be made with a greater degree of certainty. Though increased bronchial responsiveness is a useful adjunct to the diagnostic profile of asthma, at any given moment only two thirds of clinically diagnosed asthmatic subjects respond in this way and up to one third of subjects with increased bronchial responsiveness have no symptoms.[1–4] In addition, reductions in baseline airway calibre and indices of responsiveness are continuous variables, so before making a diagnosis of asthma based on these measurements, it is necessary to decide how much reversibility of airway calibre or increase in bronchial responsiveness equates with asthma, and to define a cut off point that differentiates normal from abnormal.

A clinical assessment of airway responsiveness in a patient presenting with respiratory symptoms but with normal or near normal basal pulmonary function may provide useful additional information. In adults it is most often measured using inhaled methacholine or histamine as the provoking stimulus, by challenge tests for which detailed protocols and limits of repeatability have been clearly defined. In children an exercise test is more commonly done as this form of challenge is better accepted by this age group, and perhaps has more clinical relevance because physical activity plays an important part in most children's lives. Indeed, exercise challenge forms part of the assessment of the child with respiratory symptoms in many outpatient clinics.

Few comparisons have been made between exercise and methacholine or histamine as the provoking stimulus in bronchial challenge, and those that have do not only lack standardisation of methods, making comparisons between studies difficult, but have also been conducted on highly selected 'stable' groups of asthmatic patients.[5–8] If two procedures are to be compared for their diagnostic potential, it is imperative that the studies be undertaken in the population in which the discriminant test is to be used.

In the present study we have assessed the relationship of increased bronchial reactivity to exercise and to methacholine challenge in a group of 7–8 year old children with recurrent respiratory symptoms who were identified from a normal population by questionnaire. In this way the subjects were chosen so that they best represented the clinician's dilemma—children who had respiratory symptoms that might or might not be caused by asthma. Tests of airway responsiveness to both exercise and methacholine were done to see if there was any association between them in children with symptoms. In addition, we examined the influence of atopy on the two indices of airway responsiveness in these children.

Subjects and methods

SELECTION OF SUBJECTS

As part of a larger epidemiological study, the families of all 7 and 8 year old children registered on the lists of 86 local general practitioners were sent a questionnaire about respiratory symptoms. The relevant questions were:

- Has your child had an attack of wheezing at any time during the last 12 months?
- In the last 12 months, has your child seemed to cough more (or to get more coughs) than other children?
- In the last 12 months, has your child woken at night coughing for three or more consecutive nights (apart from during the first five days of a cold)?

A randomly selected sample of the symptomatic subjects was invited to join this study. The families were approached by telephone, or by a letter that included a reply slip and postage paid envelope. Reminder letters were sent after four weeks if no reply had been received. The study was approved by the Southampton hospitals and university ethics committee.

METHODS

Appointments were made for the families to attend the laboratory at the same time of day on two consecutive days. All appointments were outside school hours at times convenient for the families. On arrival the parent of each child was asked if they thought their child had asthma, whether their general practitioner had ever diagnosed asthma, and if their child was currently receiving any antiasthma medication. If the answer to the first or second and third questions was 'yes', the child was accepted as having asthma.

Each child underwent three investigations:

(i) Allergen skin prick testing

A drug history was taken to ensure that no child was using any preparation that might interfere with a response. Skin prick tests to histamine (1 mg/ml), saline, *Dermatophagoides pteronyssinus*, mixed grass pollens, and cat fur (Bencard) were carried out. Standardised 1 mm spring loaded lancets were used to break the skin. Extracts were blotted after one minute, and the maximum diameter of the resulting weals was measured after 10 minutes. A weal 2 mm in diameter or more to one or more of the three common allergens was taken as a positive response. In addition all children were required to have a negative response to saline and a positive response to histamine.

On completing the skin tests, the first 30 children with positive reactions and the first 30 with negative reactions went on to be challenged with exercise and with methacholine. Of these 60 children 24 were diagnosed as having asthma; all 24 receiving β_2 adrenoceptor agonists, 21 by inhalation and three orally. In addition, three of the asthmatic children were receiving sodium cromoglycate, two were inhaling corticosteroids, and one was taking theophylline orally.

The two bronchial provocation tests were done in random order so that half the subjects underwent methacholine challenge first, and the other half had the exercise challenge first. The two tests were done on consecutive days at the same time of day by the same investigator.

(ii) Methacholine bronchial challenge

Children were asked not to use their β_2 adrenoceptor agonists for six hours before each test. All other medication was withheld for 24 hours.

Methacholine challenge was done by the method described by Yan *et al.*[9] The method was modified in the following ways: De Vilbiss 40 hand held glass nebulisers with known consistent outputs were selected by measuring the outputs of 10 nebulisers containing 1 ml 0·9% sodium chloride by weighing them before and after 10 activations; this was repeated 10 times. For each nebuliser the mean output and the coefficient of variation was calculated. The five nebulisers with the smallest coefficients were used in the subsequent challenges.

Solutions of methacholine in 0·9% sodium chloride were made up for each nebuliser taking into account the mean output of each instrument so that the first delivered exactly 0·025 μmol, the second 0·1 μmol, the third 0·4 μmol, and the fourth 0·8 μmol/activation. The remaining nebuliser was used to give 0·9% sodium chloride.

At the first visit, forced expiratory volume in one second (FEV_1) was measured to obtain two baseline readings within 100 ml of each other. If these exceeded 60% of the predicted for height and age, the challenged proceeded. The children were instructed in the use of the nebulisers. Once the investigator was satisfied that the child could carry out the procedure correctly, two puffs of saline were given and the FEV_1 was measured one minute later. Provided that the child's FEV_1 did not fall by more than 10% of the baseline value, the procedure was repeated using incremental doubling doses of methacholine from 0·025 μmol to 6·4 μmol, until either the FEV_1 fell by more than 20% of the baseline value, or the final dose was reached. The percentage fall in FEV_1 measured after the saline had been given was plotted against the cumulative dose of methacholine on a log scale. The dose of methacholine that caused a 20% fall in FEV_1 (PD_{20}) was derived from linear interpolation of the last two points. For subjects in whom they lay between 6·4 and 12·8 μmol, PD_{20} values were calculated by extrapolation. On completing the challenge, 100 μg of salbutamol was given by inhalation from a spacer device to restore airway calibre.

(iii) Exercise challenge

Children were allowed to proceed to exercise challenge if their FEV_1 was more than 60% of the predicted normal. The exercise challenge comprised treadmill running on a Powerjog treadmill (Sport Engineering), which was programmed to operate at a speed of 4·8 kph and a gradient of 15°. The children exercised for six minutes. Their heart rates were measured with a three electrode yoke and cardiorater (Cardiac Recorders Ltd) to ensure that all subjects exercised to 90% of their age predicted maximum heart rate. Temperature in the exercise laboratory was kept between 22 and 24°C. On completion of the exercise FEV_1 was measured at 3, 5, and 10 minutes. Salbutamol 100 μg was then given by a spacer device. The airways response to exercise was plotted as the percentage fall in FEV_1 from baseline against time, and the maximum fall within the 10 minute period was used for analysis.

STATISTICAL METHODS

The number required to give a correlation coefficient of 0·5 at the 5% level of significance was calculated. Thirty pairs of observations were shown to be adequate to do this with 80% power.

Because of the need to include censored values, and the skewed distribution of the values for the non-atopic subjects, non-parametric tests were used throughout. Spearman's rank correlation was used to examine the association between methacholine and exercise challenges separately for the atopic and the non-atopic children. In addition, the association between a positive methacholine challenge (PD_{20} <6·4 μmol) and a positive exercise challenge (maximum fall in FEV_1 after exercise <15%) was examined and odds ratios were calculated. These arbitrary cut off points were chosen because they were most commonly used by other workers.[10–14] The specificity and sensitivity of each of the two challenges for detecting asthma were calculated. The Mann-Whitney U test was used to compared the responses of the atopic and non-atopic children for each challenge. 95% Confidence intervals (CI) were calulated where appropriate.

Results

Of those initially approached, 89% of parents allowed their children to be investigated. Two children were unable to do technically adequate FEV_1 tests; they were both small girls, who reached their forced vital capacity in less than one second, and so were excluded from further testing.

The results were analysed for 30 atopic and 30 non-atopic children, all of whom completed both challenge tests. The ratio of boys to girls between the atopic and non-atopic groups was 5:1 and 1:1·3, respectively. The excess of boys in the atopic group was a result of the increased interest in sport among boys of this age compared with girls; the initial approach stressed the exercise content of the study, and boys were not only more likely to have had exercise induced bronchospasm because of their regular participation in team sports, but were also more willing to do the required tests. In addition, the increased proportion of boys in this study reflects the increased incidence of respiratory symptoms and asthma in this age group.

METHACHOLINE PROVOCATION

The atopic subjects were significantly more responsive to inhaled methacholine than those who had negative skin tests (fig 1). Of the 30 atopic children, only three had a PD_{20} >6·4 μmol, compared with 20 of those who were non-atopic. The median PD_{20} for the atopic group was 0·55 μmol whereas that for the non-atopic group was >12·8 μmol, the difference being highly significant ($p<0·001$). The odds ratios for the association between atopy and a positive methacholine challenge was 13·5 ($p<0·001$, 95% CI 3·3 to 54·7).

EXERCISE PROVOCATION

The atopic children also showed a greater response to exercise than those who were non-atopic (fig 2). Ten of the 30 atopic children achieved a fall in FEV_1 of >15% after exercise compared with only four of those who were non-atopic. The median fall in FEV_1 was 9·9% for the atopic children and 4·8% for the non-atopic children, the difference being significant ($p=0·02$, 95% CI 1·3 to 14·2). The odds ratio for the association between atopy and a positive exercise challenge was 3·3 ($p=0·13$, 95% CI 0·9 to 11·9).

Of the 24 subjects with diagnosed asthma, 21 were atopic and the odds ratio for the association between atopy and asthma was 21·0 ($p<0·001$, 95% CI 5·0 to 87·4). Twenty achieved a PD_{20} of methacholine of <6·4 μmol (fig 3). Of these, seven responded to exercise with a >15% fall in FEV_1. No asthmatic child

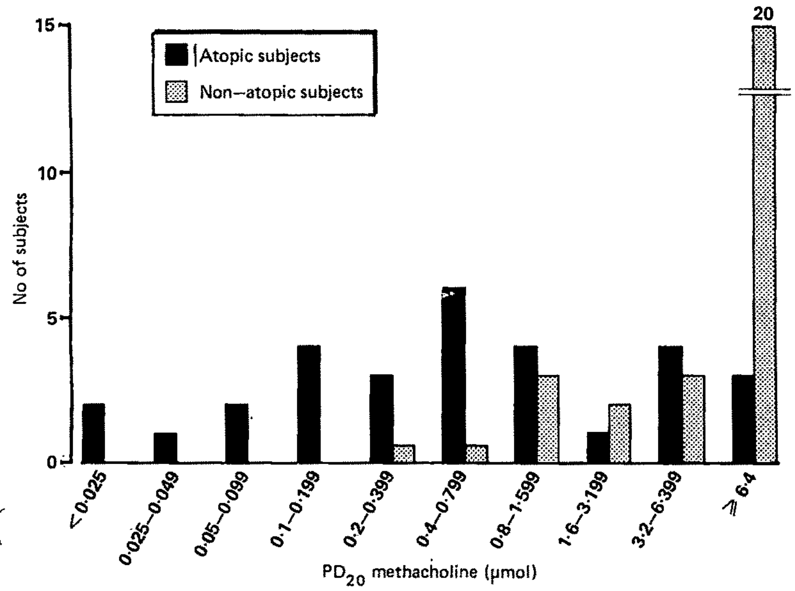


Figure 1 Response of atopic and non-atopic subjects to methacholine.

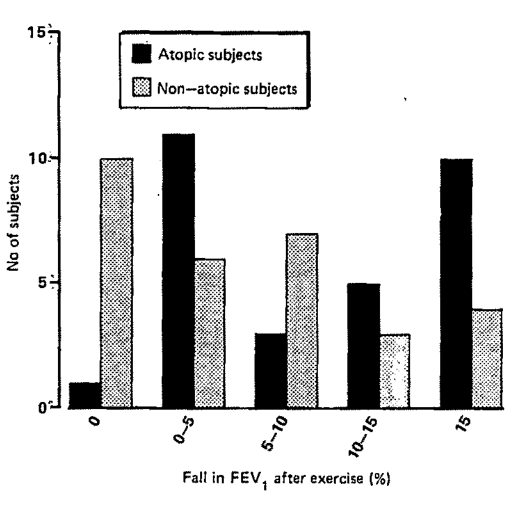


Figure 2 Response of atopic and non-atopic subjects to exercise.

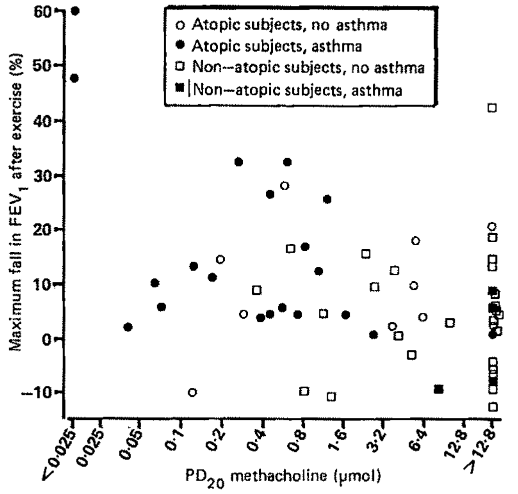


Figure 3 Maximum percentage fall in FEV$_1$ after exercise plotted against PD$_{20}$ methacholine (µmol) for atopic and non-atopic subjects divided according to whether or not they had asthma.

responded to exercise alone. Of the 36 remaining subjects, 19 achieved a PD$_{20}$ of methacholine of <6·4 µmol, and of these, three also responded to exercise. In this group, four children responded to exercise alone with a >15% fall in FEV$_1$. The sensitivity of methacholine challenge was 83% and the specificity 47%. The sensitivity of exercise challenge was 29% and the specificity 81%.

ASSOCIATION BETWEEN METHACHOLINE AND EXERCISE CHALLENGE

Figure 3 shows the association between the results of exercise and methacholine challenge testing. When testing the association between exercise and methacholine, the Spearman rank correlation gave $r_s=0·04$ ($p=0·84$) for the atopic group and $r_s=0·26$ ($p=0·17$) for the non-atopic group. Thus in neither group was there evidence to support the existence of an association significant at the 5% level. These results were supported by calculation of odds ratios for individual subjects who had both positive exercise and methacholine challenges; the odds ratio for the atopic group was 1·0 (95% CI 0·1 to 12·6) and for the non-atopic group 1·6 (95% CI 0·2 to 13·2).

Discussion

In a group of children with recurrent respiratory symptoms we could find no significant correlation at the 5% level between the response of the bronchi either to inhaled methacholine or to exercise, although the children with positive skin tests were significantly more sensitive to both stimuli.

This does not support the findings of other studies, which have shown an association between the results of the two challenges.[6 8] Previous studies, however, have studied groups with stable mild or moderate asthma and normal subjects. The group of children that we have studied consisted of subjects with symptoms, but they were not preselected because of a diagnosis of asthma.

We made every attempt to exclude as many factors as possible that might have a confounding influence on the testing procedure. All testing was performed by the same investigator; the order of the two challenge procedures was randomised; the two tests were done at the same time of day to avoid any circadian effect on bronchial reactivity, and on consecutive days to minimise the effect of any changes resulting from exposure to allergens or viral infection; all testing was done before the pollen season; and measures were taken to ensure maximum effort in carrying out the FEV$_1$—readings were repeated until two technically adequate recordings within 100 ml of one another were obtained.

In common with other published reports on exercise challenge a single period of exercise was undertaken.[5–7] This was in contrast to the way in which methacholine was given; we chose to give it in cumulative, incremental doses, as this is standard procedure in our department and we have done more than 2000 such challenges in young children without incident. An alternative would have been to predetermine the PD$_{20}$ of methacholine and then to have given that dose as a single inhalation, but airway responsiveness can vary significantly over short periods of time, and so for reasons of safety and to enable us to compare two methods of bronchial challenge in current use, we preferred to deliver cumulative doses of methacholine.

A PD$_{20}$ of <6·4 µmol methacholine was regarded as representing a positive challenge. Although any level of airway responsiveness that is chosen to represent the cut off between 'normal' and 'abnormal' in a group in which responsiveness to methacholine is a normally distributed phenomenon will of necessity be arbitrary, the definition of increased bronchial responsiveness used in this study (PD$_{20}$ <6·4 µmol) is widely used,[1–9] and our conclusions would not have differed if <12·8 µmol had been taken as the cut off point.

The standardisation of exercise challenge is not easy. In this study we ensured that the degree of exercise was enough to cause an increase in heart rate to >90% of the age predicted maximum in all subjects. Pulmonary function testing was not done during exercise as the use of a mouthpiece and nose clip was unacceptable to the children. Though these are regarded as standard in exercise challenge tests in adults—both to ensure mouth breathing and to allow investigation of the expired gases—this is not the case in paediatric practice. A review of the other studies available[10–14] showed that none had used nose clips; that various types of exercise were used that are inferior to treadmill running[10 11 13]; and though most ensured that heart rate did increase to a preselected percentage of the age predicted maximum at some time during exercise,[12–14] some failed to monitor heart rate in half[10] or all[11] subjects. Warm air represents a less potent stimulus to the bronchial tree than cold air, and the temperature in our exercise laboratory was 22–24°C. This may explain our relatively low incidence of exercise induced bronchospasm compared with the 63–71% found in other studies done on children of similar age. This finding might, however, be a reflection of selection; children selected from a community based survey are likely to have less severe symptoms than those attending hospital.

Exercise induced bronchospasm is not an invariable feature of asthma, nor is it exclusive to asthma. It can occur in conjunction with cystic fibrosis,[15] with a history of previous asthma,[16] and in normal subjects.[11 12] Konig and Godfrey have, however, shown that there is an increased prevalence in the relatives of asthmatic subjects,[17 18] and a higher concordance between pairs of monozygotic twins compared with dizygotic twins.[19] This suggests that it is an inherited phenomenon, and is inherited independently of atopy. In view of the established genetic association between atopy and asthma,[20] and that between asthma and exercise induced bronchospasm, it is not surprising that it was over three times more common in atopic than in non-atopic children. The question is therefore: what disease is causing the bronchospasm, the reaction to methacholine and the respiratory symptoms in the non-atopic children? Asthma is a clinical syndrome, and as such may represent a range of diseases with different causes. Within that range there may be a subgroup of children without atopy who demonstrate symptoms only when provoked by specific stimuli such as viral respiratory tract infections.[21] It has been suggested that children with such symptoms may lose them as they become older because atopy is necessary for symptoms to persist into adult life. Although viral respiratory infections may be the primary stimulus in these children, they may also be more susceptible to other respiratory stimuli, both specific and non-specific.

We have failed to show a significant association between exercise induced and methacholine responsiveness, both when the complete data were examined, and when 'positive' responses alone were analysed. This might have been because of the heterogeneity of the study group and, indeed, the studies that have shown such an association have usually preselected their subjects. The relatively poor reproducibility of exercise challenge testing may also be a contributory factor.[22]

An alternative explanation lies in the mode of action of the stimuli used, as different stimuli may act through different bronchoconstricting mechanisms. Pauwels *et al* have suggested that the term 'non-specific' when applied to increased bronchial responsiveness is no longer adequate to cover both the pharmacological and the physical stimuli that can result in an increased bronchoconstrictor response of the airways.[23] They suggested that a distinction should be made between those non-specific stimuli that act directly on the smooth muscle, of the airways and those that affect structures other than the smooth muscle, such as mast cells and neurones. The examples they cited were exercise, adenosine, and neurokinin A, and they suggested that these types of stimuli should be designated 'direct' and 'indirect'. Testing with both types of stimuli might perhaps be of use in clinical practice, but the results of such testing must be interpreted in the light of the increasing evidence of their lack of specificity in diagnosing asthma. It could be argued that exercise testing should be preferred to chemical stimuli because of its environmental relevance.

These results emphasise that exercise induced bronchospasm is not simply an index of non-specific bronchial responsiveness. Asthma is a complex group of heterogeneous diseases, and care must be taken when interpreting the results of studies in which the subjects were selected to represent a single facet of the disease. Using different stimuli to challenge the airways will supply different answers, and as Pauwels *et al* suggest, the use of both 'direct' and 'indirect' stimuli in longitudinal epidemiological studies of bronchial responsiveness will shed more light on both the pathogenesis of asthma and the relevance of bronchial responsiveness.

1 Burney PGJ, Britton WJ, Chin S, Tattersfield AE, Papacosta AO. Descriptive epidemiology of bronchial reactivity in an adult population; results from a community survey. *Thorax* 1987;42:38–44.

2 Sears MR, Jones DT, Holdaway MD. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986;41:283–9.

3 Salome CM, Peat JK, Britton WJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren: I. relation to respiratory symptoms and diagnosed asthma. *Clinical Allergy* 1987;17:271–82.

4 Hopp RJ, Bewtra AK, Nair NM, Watt GD, Townley RG. Methacholine inhalation challenge studies in a selected paediatric population. *Am Rev Respir Dis* 1986;134:994–8.

5 Chatham M, Bleeker ER, Smith PL. A comparison of histamine, methacholine and exercise airway reactivity in normal and asthmatic subjects. *Am Rev Respir Dis* 1982; 126:235–40.

6 Kiviloog J. Bronchial reactivity to exercise and methacholine in bronchial asthma. *Scandinavian Journal of Respiratory Disease* 1973;54:347–58.

7 Anderton RC, Cuff MT, Frith PA, *et al.* Bronchial responsiveness to inhaled histamine and exercise. *J Allergy Clin Immunol* 1979;63:315–20.

8 Eggleston PA. A comparison of the asthmatic response to methacholine and exercise. *J Allergy Clin Immunol* 1979;63: 104–10.

9 Yan K, Salome C, Woolcock A. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;38:1–5.

10 Tsanakas JN, Milner RDG, Bannister OM, Boon AW. Free running asthma screening test. *Arch Dis Child* 1988;63: 261–5.

11 Kawabori I, Pierson WE, Conquest LL, Bierman CW. Incidence of exercise-induced asthma in children. *J Allergy Clin Immunol* 1976;58:447–55.

12 Kattan M, Keens TG, Mellis CM. The response to exercise in normal and asthmatic children. *J Pediatr* 1978;92:718–21.

13 Cropp GJA. Grading, time-course and incidence of exercise induced airway obstruction and hyperinflation in asthmatic children. *Pediatrics* 1975;56:868–9.

14 Mellis CM, Kattan M, Keens TG, Levison H. Comparative studies of histamine and exercise challenges in asthmatic children. *Am Rev Respir Dis* 1978;117:911–5.

15 Mellis CM, Lenson H. Bronchial reactivity in cystic fibrosis. *Pediatrics* 1978;61:446–50.

16 Blackhall MI. Ventilatory function in subjects with childhood asthma who have become symptom-free. *Arch Dis Child* 1970;45:363–6.

17 Konig P, Godfrey S. Prevalence of exercise-induced bronchial lability in families of children with asthma. *Arch Dis Child* 1973;48:513–8.

18 Konig P, Godfrey S. Exercise-induced bronchial lability and atopic status of families of infants with wheezy bronchitis. *Arch Dis Child* 1973;48:942–6.

19 Konig P, Godfrey S. Exercise-induced bronchial lability in monozygotic (indentical) and dizygotic (non-identical) twins. *J Allergy Clin Immunol* 1974;54:280–7.

20 Cookson WOCM, Musk AW, Ryan G. Associations between asthma history, atopy and non-specific bronchial responsiveness in young adults. *Clinical Allergy* 1986;16:425–32.

21 Clifford RC, Howell JB, Radford M, Holgate ST. Associations between respiratory symptoms, bronchial responsiveness to methacholine, and atopy in two age-groups of schoolchildren. *Arch Dis Child* 1989;64:1133–9.

22 Godfrey S, Silverman M, Anderson S. Problems of interpreting exercise-induced asthma. *J Allergy Clin Immunol* 1973; 52:199–209.

23 Pauwels R, Joos G, Van der Straeten M. Bronchial hyperresponsiveness is not bronchial hyper-responsiveness is not bronchial asthma. *Clinical Allergy* 1988;18:317–21.

Archives of Disease in Childhood 1991; 66: 584–587

Is low birth weight a risk factor for asthma during adolescence?

D S Seidman, A Laor, R Gale, D K Stevenson, Y L Danon

Abstract

The effect of low birth weight on the incidence of asthma by 17 years of age was investigated by studying medical draft examination records of 20 312 male subjects born in Jerusalem between January 1967 and December 1971. Additional information on birth weight and other demographic factors was abstracted from the Jerusalem Perinatal Study computerised database. A stepwise multiple logistic regression was used to estimate the odds ratios for developing asthma by 17 years of age in 500 g birthweight categories from <2000 g to 4500 g. The odds ratios were adjusted for the confounding effects of ethnic origin, social class (determined by area of residence), paternal education, maternal age, and birth order. The group with low birth weights (<2500 g, n=1004) had a significantly increased risk of developing asthma by 17 years of age, with an adjusted odds ratio of 1·44 (95% confidence interval (CI) 0·79 to 2·66) for birthweight group <2000 g and 1·49 (95% CI 1·05 to 2·12) for birthweight group 2000–2499 g compared with the reference group of 3000–3499 g.

We conclude that infants with birth weights of <2500 g may have a higher risk of asthma during childhood and adolescence than infants who were heavier at birth.

Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer 52621, Israel
D S Seidman

Medical Statistics Branch, Israeli Defence Force Medical Corps
A Laor

Department of Neonatology, Bikur Cholim Hospital, Jerusalem, Israel
R Gale

Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA
D K Stevenson

Division of Pediatric Immunology, Belinson Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel
Y L Danon

Correspondence to:
Dr Seidman.

Accepted 13 December 1990

Advances in neonatal intensive care have greatly improved the survival of low birthweight (LBW) infants, but they still have a high risk of handicaps.[1 2] Currently little is known about the long term respiratory outcome of LBW infants. Chan *et al* reported a close association between low birth weight and poor airway function,[3] and troublesome cough at 7 years of age.[4]

The aim of this study was to evaluate the influence of low birth weight on the incidence of asthma during childhood and adolescence. The possible effects of social, ethnic, and environmental factors were taken into account.

Subjects and methods

The computerised records of the medical examinations of 20 312 male recruits to the Israeli army who were born in Jerusalem between 1964 and 1971 were reviewed to establish the incidence of asthma. Each subject had been asked specifically whether he had ever been diagnosed as having asthma and whether he had ever had recurrent wheezing, nocturnal coughing, or coughing or wheezing after exertion (I Auerbach, C Springer, S Godfrey, personal communication). All those with any symptoms that could have been indicative of past or present asthma were referred for a second examination by a pulmonologist. This examination included a further detailed history, physical examination, and spirometry while at rest. An exercise test was done during the latter period of our study in all subjects except those who had overt signs of obstruction on spirometry. The specific information about lung function information is not available, however, as the computerised data included only the final diagnosis.

Asthma was diagnosed only in cases with clear medical evidence of past or present bronchial disease, as opposed to episodic attacks. Birth weights recorded at the time of delivery were obtained from the computerised files of the Jerusalem Perinatal Study.[5 6] Detailed demographic data were available from the computerised records of the military draft medical examination.[7] The data for each individual were matched using a seven digit identification number. The completeness of the match was confirmed by comparing maternal identity numbers.

A stepwise multiple logistic regression analysis was done with the Logist procedure of the SAS software to adjust for the effect of the studied independent variables.[8] Asthma was used as the dependent variable. The independent variables were birth weight (in 500 g categories from <2000 g–4500 g), ethnic origin (according to paternal country of birth), area of residence (classified by municipal tax level),[6] maternal age (as a continuous variable), paternal educational attainment (years of schooling) and birth order (categorised to avoid dubious assumptions about linearity). All variables that were significant ($p<0·05$) were added to a model that contained the birth weight variable at the first step.

The results of the logistic regressions are presented as adjusted odds ratios with their 95% confidence intervals (CI). The estimates presented are based on the exclusion of cases with missing values (1·9%).

Results

The overall incidence of asthma in our study population at 17 years of age was 3·7%. Subjects whose birth weight was between 2000–2499 g had a significantly higher incidence of asthma. Other factors that were associated with a significantly increased risk of asthma included European or North American ethnic origin, being the first born, and having a well educated father (table 1). There was a significantly lower incidence of asthma among subjects who were of Asian origin, who were high in the birth order, and whose fathers were less well educated (table 1). Obesity and area of residence were not related to the incidence of asthma.

To estimate the risk of asthma associated with birth weight a multiple logistic regression analysis was used to control for the effects of confounding variables. All the variables listed in table 1 were analysed. The final model reached by the stepwise procedure included the birth weight variable and four confounding variables: birth order, paternal education, maternal age, and ethnic origin. Logistic analysis of these data confirmed that there was a highly significantly increased risk of asthma at 17 years of age for those with birth weights of less than 2500 g (table 2).

Table 1 Distribution of population characteristics and incidence of asthma at 17 years of age among 20 312 male subjects born in Jerusalem, 1967–71

Population characteristics	*Percentage of total population*	*Percentage with asthma*
Ethnic origin (paternal country of birth):		
Israel	14·9	3·8
Asia	33·3	2·7*
Africa	23·5	3·3
Europe or North America	28·3	4·8*
Paternal educational attainment (years of schooling):		
<8	37·2	2·7*
8–12	38·7	4·1*
>12	24·1	5·1
Birth order:		
1	28·2	5·0*
2	23·3	3·9
3–4	26·8	3·4
≥5	21·7	2·0*
Area of residence (municipal tax level):		
High	26·3	4·1
Medium	33·8	4·0
Low	39·9	3·0
Birth weight (g):		
<2000	1·1	5·8
2000–2499	3·6	5·3**
2500–2999	16·3	4·1
3000–3499	41·2	3·6
3500–3999	28·8	3·4
4000–4499	7·8	3·5
>4500	1·2	3·9
Body mass index (kg/m^2):		
>24·6	10·2	4·2
≤24·6	89·8	3·6
Total	100	3·7

*p<0·001; **p<0·01 (χ^2 test).

Discussion

The present study is the first to our knowledge that examines the incidence of asthma in association with birth weight in a large population for a period of 17 years. Low birth weight was associated with asthma diagnosed up to 17 years of age. Such an association has been suggested previously,[9] and the need for long term follow up was stressed.[10] Most previous studies have shown that small groups of infants who survive specific neonatal respiratory complications and treatments, including bronchopulmonary dysplasia,[11, 12] hyaline membrane disease,[13–15] or artificial ventilation have reduced airway function.[16–19] In some studies, however, impairment in lung function has been observed in healthy LBW infants as well.[20] Furthermore, long term follow up studies extending to school age have shown that abnormal lung function is not unusual among LBW children.[3, 4, 17, 18, 21] The association between low birth weight and poor airway function is independent of neonatal respiratory illness, oxygen treatment, or mechanical ventilation.[3, 4] Perinatal factors, including the amount of respiratory support, were found to make only a small contribution to the reduction in airway function found in children of low birth weight at the ages of 7[22] and 9[23] years.

A number of possible explanations for the link between low birth weight and asthma have been proposed. The reduced airway function has been attributed to constitutional factors, prematurity itself, or other undetermined factors.[23] The airway hyperactivity found at 7 and 12 years of age in prematurely born children without neonatal lung disease, led Bertrand *et al* to speculate that unexplained premature labour may share a common pathway with airway lability.[24] In the present study we could not take into account the family history of asthma. Chan *et al*, in a prospective study on a cohort of 7 year old children of low birth weight, found an increased prevalence of airway responsiveness to histamine that was significantly related to a history of asthma in siblings,[25] but they were unable to confirm the hypothesis that maternal smooth muscle irrita-

Table 2 Adjusted odds ratios for asthma at 17 years of age by birth weight, ethnic origin, area of residence, maternal age, paternal education, and birth order for 20 312 male subjects born in Jerusalem, 1964–71

Variable	*No of subjects*	*Adjusted odds ratios*	*95% confidence intervals*
Birth weight (g):			
<2000	223	1·44	(0·79 to 2·62)
2000–2499	781	1·49 (p<0·001)	(1·05 to 2·12)
2500–2999	3311	1·09	(0·89 to 1·35)
3000–3499*	8369	1·00	
3500–3999	5160	0·97	(0·81 to 1·17)
4000–4499	1584	1·11	(0·83 to 1·49)
>4500	244	1·30	(0·73 to 2·67)
Birth order:			
1	5727	0·72 (p<0·001)	(0·59 to 0·89)
2*	4733	1·00	
3–4	5444	0·58 (p<0·001)	(0·47 to 0·73)
≥5	4408	0·33 (p<0·001)	(0·24 to 0·45)
Paternal education (years):			
<8	7556	†	
8–12*	7861	1·00	
>12	4895	1·33 (p<0·001)	(1·13 to 1·58)
Ethnic origin:			
Israel*	3027	1·00	
Asia	6764	0·81 (p<0·05)	0·66 to 0·99)
Africa	4773	†	
Europe or North America	5748		

*Reference group; †variable not significant in the final logistic model.

bility (uterine and bronchial) has a causative role in either the premature labour or in the subsequent airway hyper-responsiveness in the prematurely born infants.

The excess risk of asthma may also be the outcome of acute lower respiratory tract infections in infancy including bronchitis, bronchiolitis and pneumonia,[26–28] which are known to be more common among LBW children.[12] Asthma has also been related to other diseases of infancy including throat or ear infections, eczema, and allergic rhinitis,[29] all reported more frequently among LBW infants.[30]

Area of residence, social class, and family size are associated with a history of upper[31] and lower[32–35] respiratory tract infections. Because the incidence LBW infants is increased among families in low socioeconomic groups,[36 37] poor environmental conditions may explain the observed link between LBW and asthma in childhood and adolescence. It is interesting to note that while Burr found that having more siblings increased the likelihood of prolonged colds, and of wheeze and nasal discharge.[38] Strachan showed a strong inverse relationship between hay fever and the number of children in the household at the age of 11.[39] The present results show a decreased risk of asthma for children of high birth order, which accords with the atopic nature of the disease. The higher incidence of asthma in smaller households may be a possible explanation for the current increase in the prevelance of asthma.[8 38 39]

Maternal smoking in pregnancy is a major determinant of birth weight,[36 40] and its intrauterine effects may be related to lower respiratory tract illness in early life.[41] Furthermore, LBW infants affected by maternal and environmental (passive) smoking antenatally are more likely to be exposed to tobacco smoke during childhood.[42] This may lead to an increased incidence of respiratory illness[43] and aggravation of asthma.[38 44 45] Data on the incidence of smoking among our sample was not available, but as adolescents born to mothers that smoke are more prone to do so themselves, they are also more likely to have been born with a lower birth weight and subsequently to have bronchial disease as a result of their smoking. Smoking by both the mothers and the subjects themselves may thus confound the association between low birth weight and asthma.

Birth weight could not be corrected for gestational age in the present sample, so it was not possible to find out if the increased risk of asthma was related to intrauterine growth retardation or immaturity. Nevertheless, low birth weight remains an important indicator of neonatal outcome.

In the present study, a large population from a geographically defined area was evaluated. The results may thus reflect the later effect of low birth weight on pulmonary function in relation to the incidence in our population. Population studies are important, as estimates of the incidence of asthma in childhood vary widely as a result of the different diagnostic labels given.[46 47] Our findings indicate that LBW infants have an increased risk of asthma in childhood and adolescence. Further research is necessary to improve our understanding of the factors that predispose low birthweight infants to asthma in later life.

We acknowledge financial assistance from the Doron Foundation.

1 Vohr BR, Garcia Coll CT. Neurodevelopment and school performance of very low birthweight infants: a seven-year longitudinal study. *Pediatrics* 1985;**76**:345–50.

2 Lloyd BW, Wheldall K, Perks D. Controlled study of intelligence and school performance of very low-birth weight children from a defined geographical area. *Dev Med Child Neurol* 1988;**30**:36–42.

3 Chan KN, Noble-Jamieson CM, Elliman A, *et al.* Lung function in children of low birth weight. *Arch Dis Child* 1989; **64**:1284–93.

4 Chan KN, Elliman A, Bruyan E, Silverman M. Respiratory symptoms in children of low birth weight. *Arch Dis Child* 1989;**64**:1294–304.

5 Davies AM, Prywes R, Tzur B, *et al.* The Jerusalem Perinatal Study. 1. Design and organization of a continuing, community-based, record-linked survey. *Isr J Med Sci* 1969;**5**:1095–101.

6 Harlap S, Davies AM, Grover NB, Prywes R. The Jerusalem Perinatal Study: the first decade 1964–1973. *Isr J Med Sci* 1977;**13**:1073–82.

7 Kark JD, Kedem R, Revach M. Medical examination of Israeli 17-year-olds before military service as a national resource for health information. *Isr J Med Sci* 1986;**22**: 318–25.

8 SAS Institute Inc. *SUGI supplemental library users' guide. Version 5.* Cary: SAS Institute Inc, 1986:269–93.

9 Noble-Jamieson CM, Lukeman D, Silverman M, Davies PA. Low birth weight children at school age: neurological, psychological, and pulmonary function. *Semin Perinatol* 1982;**6**:266–73.

10 Davies PA. Follow up of low birthweight children. *Arch Dis Child* 1984;**59**:794–7.

11 Smyth JA, Tabachnik E, Duncan WJ, *et al.* Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia. *Pediatrics* 1981;**68**:336–40.

12 Vohr BR, Bell EF, Oh W. Infants with bronchopulmonary dysplasia. *Am J Dis Child* 1982;**136**:443–7.

13 Heldt GP, MucIllory MB, Hansen TN, *et al.* Exercise performance of the survivors of hyaline membrane disease. *J Pediatr* 1980;**96**:995–9.

14 Stahlman M, Hedvall G, Lindstrom D, *et al.* Role of hyaline membrane disease in production of later childhood lung abnormalities. *Pediatrics* 1982;**69**:572–6.

15 Driscoll DJ, Kleinberg F, Heise CT, *et al.* Cardiorespiratory function in asymptomic survivors of neonatal respiratory distress syndrome. *Mayo Clin Proc* 1987;**62**:695–700.

16 Dinwiddie R, Mellor DH, Donaldson SHC, Tunstall ME, Russell G. Quality of survival after artificial ventilation of the newborn. *Arch Dis Child* 1974;**49**:703–10.

17 Borkenstein J, Borkenstein M, Rosegger H. Pulmonary function studies in long-term survivors with artificial ventilation in the neonatal period. *Acta Paediatr Scand* 1980;**69**: 159–63.

18 Riedel F. Long-term effects of artificial ventilation in neonates. *Acta Paediatr Scand* 1987;**76**:24–9.

19 Andreasson B, Lindroth M, Mortensson W, Svenningsen NW, Jonson B. Lung function eight years after neonatal ventilation. *Arch Dis Child* 1989;**64**:108–13.

20 Coates AL, Bergsteinsson H, Desmond K, *et al.* Long-term pulmonary sequelae of premature birth with and without idiopathic respiratory distress syndrome. *J Pediatr* 1977; **90**:611–6.

21 Mansell AL, Driscoll JM, James LS. Pulmonary follow-up of moderately low birthweight infants with and without respiratory distress syndrome. *J Pediatr* 1987;**110**:111–5.

22 Chan KN, Elliman A, Bryan E, Silverman M. Clinical significance of airway responsiveness in children of low birth weight. *Pediatr Pulmonol* 1989;**7**:251–8.

23 Chan KN, Wong YC, Silverman M. Relationship between infant lung mechanics and childhood lung function in children of very low birth weight. *Pediatr Pulmonol* 1990;**8**: 74–81.

24 Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyperreactivity and the respiratory distress syndrome. *N Engl J Med* 1985;**312**:742–5.

25 Chan KN, Noble-Jamieson CM, Elliman A, *et al.* Airway responsiveness in low birth weight children and their mothers. *Arch Dis Child* 1988;**63**:905–10.

26 Gurwitz D, Mindorff C, Levison H. Increased incidence of bronchial reactivity in children with a history of bronchitis. *Pediatrics* 1981;**98**:551–5.

27 Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ* 1982;**284**:1665–9.

28 Mok JYQ, Simpson H. Outcome for acute bronchitis, bronchiolitis, and pneumonia in infancy. *Arch Dis Child* 1984; **59**:306–9.

29 Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Community Health* 1986;**40**:121–9.

30 Overpeck MD, Moss AJ, Hoffman HJ, Hendershot GE. A comparison of the childhood health status of normal birth-

weight and low birthweight infants. *Public Health Rep* 1989;**104**:58–70.

31 Burr ML, Miskelly FG, Butland BK, *et al*. Environmental factors and symptoms in infants at high risk of allergy. *J Epidemiol Community Health* 1989;**43**:125–32.

32 Holland WW, Halil T, Bennett AE, Elliott A. Factors influencing the onset of chronic respiratory disease. *BMJ* 1969;**ii**:205–8.

33 Colley JRT, Douglas JWB, Reid DD. Respiratory disease in young adults: influence of early childhood lower respiratory tract illness social class, air pollution, and smoking. *BMJ* 1973;**iii**:195–8.

34 Barker DJP, Osmond C. Childhood respiratory infection and adult chronic bronchitis in England and Wales. *BMJ* 1986; **293**:1271–5.

35 Barker DJP, Osmond C, Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. *J Epidemiol Community Health* 1989;**43**:237–40.

36 Kleinman JC, Madans JH. The effects of maternal smoking, physical stature, and educational attainment on the incidence of low birth weight. *Am J Epidemiol* 1985;**121**: 843–55.

37 Stein A, Campbell EA, Day A, McPherson K, Cooper PJ. Social adversity, low birth weight, and preterm delivery. *BMJ* 1987;**295**:291–3.

38 Burr ML. Is asthma increasing? *J Epidemiol Community Health* 1987;**41**:185–9.

39 Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**:1259–60.

40 Brooke OG, Anderson HR, Bland JM, *et al*. Effect on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *BMJ* 1989;**298**:795–801.

41 Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987;**62**:786–91.

42 Rubin DH, Krasilnikoff PA, Leventhal JM. Effect of passive smoking on birth weight. *Lancet* 1986;**ii**:415–17.

43 Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. *Lancet* 1974;**i**:529–32.

44 O'Connell EJ, Logan GB. Parental smoking in childhood asthma. *Ann Allergy* 1974;**32**:142–5.

45 Weitzman M, Gortmaker S, Klein Walker D, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990; **85**:505–11.

46 Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *BMJ* 1983;**286**: 1256–8.

47 Hill R, Williams J, Tattersfield A, Britton J. Change in use of asthma as a diagnostic label for wheezing illness in school children. *BMJ* 1989;**299**:898.

Ban it!

The 'ban it' lobby are at it again, I see. Their target this time is toy balloons. Children sometimes inhale them, as they inhale many other things. A paper from Alberta (Ryan *et al*, *American Journal of Diseases of Children* 1990;**144**:1221–4) documents four deaths in Canada between 1983 and 1988. In the United States there were 121 childhood deaths from balloon inhalation between 1973 and 1988. The authors comment that 'protective efforts should be directed to a ban on this type of balloon'.

Most children who choke do so on food. Of those who choke on other things 90% do so on household articles, such as nails or bolts, and the remaining 10% inhale toys or other 'children's products'. Of this 10%, 43% involves balloons. Balloons are therefore 'the leading cause of paediatric choking deaths from children's products'.

Of course, if you go on subcategorising long enough almost anything can be shown to be the leading cause of something or other. Most of the road deaths in Britain not involving British, French, German, Swedish, or Italian cars probably involve Japanese cars which should, of course, therefore be banned.

I am 200% in favour of preventing childhood accidents but consider the pleasure given to so many children (and adults) by toy balloons. It is not possible to ban everything a child might put into his mouth or choke on. By all means let's educate people, children, and adults. Children choke; be careful. Don't leave things around or let them play with things they might choke on. Be careful with balloons; be careful with marbles; be careful with boiled sweets. Be careful, be careful, please be careful. But ban balloons? Must we?

ARCHIVIST

Archives of Disease in Childhood 1991; 66: 588–592

Long term follow up of renal function in IgA nephropathy

U B Berg

Abstract

Fifty one children with IgA nephropathy verified at biopsy have been followed up clinically and functionally for 0·4–16·8 years from the onset of symptoms. Renal function was evaluated by determining the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) from the clearances of inulin and para-aminohippuric acid. Fifteen (29%) of the children had raised serum creatinine concentrations at the onset. Mean GFR was significantly lower than that of controls at the first investigation. During the follow up GFR and ERPF decreased and were significantly lower than in the controls after eight years of disease. The significant fall in renal function was found in children with proteinuria and especially in boys, in whom GFR and ERPF decreased from a mean (SEM) of 117 (5) and 616 (31) at 2·8 years to 97 (6) and 509 (36) ml/min/1·73 m^2 at 7·5 years. Patients with raised serum creatinine concentrations at the onset had significantly lower GFRs, and patients with macroscopic haematuria at this time did not show decreased renal function at follow up.

In conclusion, children with IgA nephropathy do not seem to have a benign clinical course. Boys with proteinuria show a significant decrease in renal function during follow up.

IgA nephropathy was once regarded as a benign kidney disease, especially in childhood.[1–3] It is now apparent that a certain percentage of cases progress to renal failure.[4–11] Early onset of disease is considered a benign sign,[3 12 13] while proteinuria is claimed to be a marker of poor prognosis.[6 10 11 14 15] It has also been shown that males generally have a poorer prognosis than females.[10 14 16 17] There are few long term follow up studies of juvenile IgA nephropathy, particularly regarding renal function.[1 18–20] Most of these studies find no persistent reduction of glomerular filtration rate (GFR). Thus Michalk *et al* concluded that a permanent decrease in renal function seems to be exceptional during childhood.[19] The observation periods in all these series were short so Michalk *et al* conclude that prospective long term studies with regular clearance measurements are necessary for a better evaluation of the prognoses of children with IgA nephropathy. Thus the aim of the present study was to follow up renal function regularly in a group of patients with IgA nephropathy that has been verified by biopsy with an onset of disease during childhood and to relate functional changes with clinical symptoms.

Department of Paediatrics, Karolinska Institute, Huddinge University Hospital, S-141 86 Huddinge, Sweden

Correspondence to:
Dr Berg.

Accepted 30 November 1990

Patients and methods

Renal function was examined in 51 children (30 boys and 21 girls), 3–18 (median 13) years of age when first functionally investigated, who had IgA nephropathy verified at biopsy and who had no signs of systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, or liver disease. Renal function was evaluated regularly at intervals of about two to three years based on the GFR and effective renal plasma flow (ERPF). All renal function tests were peformed with the patients in stable condition without signs of current infection. The follow up period from the first appearance of symptoms ranged between 0·4 and 16·8 years with a mean of 6·5 years. Twelve patients were followed for more than 10 years from the onset of symptoms.

GFR and ERPF were determined from the clearances of inulin and para-aminohippuric acid during water diuresis, using a standard clearance technique including continuous infusions of inulin and para-aminohippuric acid after a priming dose.[21] Four 30 minute urine samples were collected by spontaneous voiding and the clearance values presented are the means of the four clearance periods.

Patients with proteinuria are those who show proteinuria on several occasions when in stable condition in between acute infections. As the investigation has been done during a 10 year period, the determinations of small amounts of albumin in urine was not performed during the first years. Proteinuria is therefore defined as a positive Albustix (Ames) test or urine albumin/creatinine ratio >10 (mg/mmol) in short term urine samples collected in the morning at 74 of the 134 renal function tests.

Inulin in blood and urine was analysed by the anthrone method[22] and para-aminohippuric acid by a modified technique of Smith *et al*.[23] Urine albumin concentration was determined by an automated immunonephelometric method (Behring Nephelometer Analyser).

The results were compared by means of the Mann-Whitney non-parametric test and paired *t* test and the results are presented as mean (SEM). The renal haemodynamic data are compared with those of 36 healthy children (16 boys and 20 girls), 3·5–20·5 (median 12·5) years of age.

Results

CLINICAL PRESENTATION

Figure 1 shows the distribution of patients with IgA nephropathy by age and sex at clinical presentation. The first symptoms were discovered at a significantly earlier age in girls than boys (7·1 (0·8) compared with 10·7 (0·6) years).

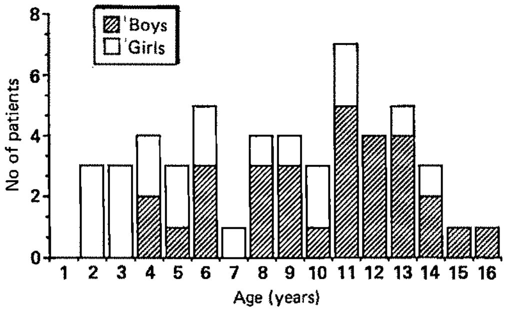


Figure 1 Age at onset and sex distribution for all children studied.

Fifteen (29%) out of 51 patients (nine boys, six girls) showed increased serum creatinine concentrations at the onset of the first symptoms. When these 15 children were first investigated with renal function tests, the GFR of five of them had already returned to normal, while the rest still had significantly ($p<0·001$) reduced GFR, ERPF, and filtration fraction (with means of 79 (5), 522 (21) ml/min/1·73 m^2 and 15·3 (1·1) %) in comparison with controls (119 (2), 627 (14) ml/min/1·73 m^2 and 19·2 (0·4) %). The GFR of five of these 10 patients returned to normal within two to four years while four (one patient has only been studied once) showed further decreases in their GFR during the follow up. One 5 year old girl who had a nephrotic syndrome at the onset of the disease progressed to terminal renal failure with GFRs of 66, 32, and 13 ml/min/1·73 m^2 at 1·4, 2·1, and 2·4 years from the onset. This girl received a renal transplant 2·6 years after the onset of the disease. The other three patients all had persistent proteinuria.

Macroscopic haematuria as a first sign of the disease was found in 22 (43%) of the 51 children, and significantly ($p<0·05$) more often among boys (17/30, 57%) than among girls (5/21, 24%). In later episodes 38 of the 51 patients (75%), 24 boys (80%) and 14 girls (67%), showed macroscopic haematuria.

Table 1 Renal haemodynamic data on the 51 children with IgA nephropathy at the first investigation in comparison with 36 healthy children (controls). Results are mean (SEM)

	IgA nephropathy (n=51)	*Controls (n=36)*
GFR (ml/min/1·73 m^2)	108 (3)*	119 (2)
ERPF (ml/min/1·73 m^2)	602 (15)	627 (14)
Filtration fraction (%)	18·3 (0·5)	19·2 (0·4)

*Indicates significant ($p<0·05$) difference between the groups.

Hypertension did not occur at the onset in any child, but three children developed hypertension during follow up. All three of these children had reduced renal function at the onset, the girl with the nephrotic syndrome at the onset and two other boys with proteinuria as well. The disease progressed in all three during follow up, and in the girl to terminal renal failure.

Serum IgA concentration was determined in 49 children. Twenty three (47%; 57% of the boys and 33% of the girls) of these children had values above the normal for their ages.

RENAL HAEMODYNAMICS

Table 1 shows the mean GFR, ERPF, and filtration fraction of the whole group in comparison with 36 healthy controls. The first renal function test selected here does not include the very first test performed in the patients with reduced GFRs when first investigated. In these patients the second investigation was chosen, when GFR had returned to normal or nearly normal. GFR was significantly decreased in the children with IgA nephropathy compared with the controls. ERPF and filtration fraction did not differ between the patients and the controls.

Figure 2 shows the GFR and ERPF of all patients at different periods of time from the onset of disease. GFR during the first two years (111 (3) ml/min/1·73 m^2) as well as after more than eight years' duration of disease (107 (3) ml/min/1·73 m^2), was significantly lower than that

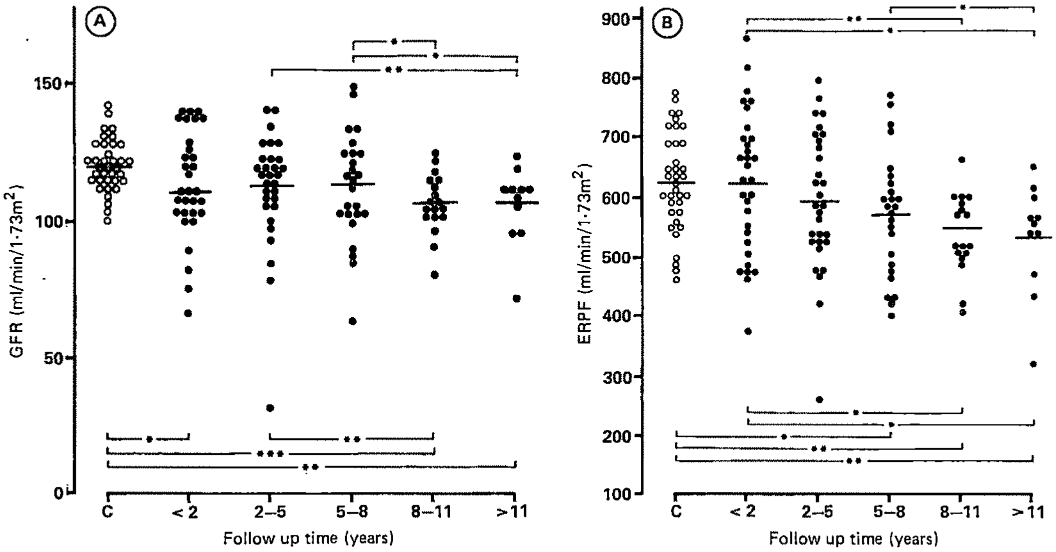


*Figure 2 (A) GFR and (B) ERPF in individual patients during follow up in different time periods from the onset of the disease. The stars above the symbols indicate significant differences calculated by the paired t test and the stars below the symbols indicate significant differences calculated with the non-parametric Mann-Whitney test; *$p<0·05$, **$p<0·01$, and ***$p<0·001$.*

of controls. A significant fall (paired *t* test) in GFR was found from five to eight to more than eight years. ERPF did not differ significantly from that of controls during the first years but was significantly lower than that of controls after five years' duration of disease. A significant decrease in ERPF, calculated by paired *t* test, was seen from abot eight years' duration of disease. Filtration fraction increased from the first two years to after five years' duration of disease.

Table 2 shows the first and last renal haemodynamic values for the 38 patients studied on more than one occasion. The first study was chosen when the initial reduction in renal function, found in some patients, had been overcome. GFR and ERPF decreased significantly during follow up to values significantly lower than those of controls. When the patients are grouped according to sex (table 2), boys show decreases in their GFR and ERPF to values significantly lower than those of controls. Girls, however, had a significantly lower GFR (113 ml/min/1·73 m^2) than that of controls from the beginning, but did not decrease their GFR further during follow up.

When the patients are grouped into those with and without proteinuria during follow up (table 2) and the nephrotic girl, whose condition progressed to terminal renal failure is excluded, the GFR and ERPF of those patients with proteinuria decreased significantly during follow up. Patients without proteinuria show no progression and have a normal GFR and ERPF throughout the follow up period. After a further grouping of the patients according to sex as well as to the occurrence of proteinuria, boys with proteinuria are the patients whose GFR and ERPF decrease during follow up to values significantly lower than those of controls. Girls with proteinuria have a significantly lower GFR and ERPF than controls at the last investigation, but, by the paired *t* test, no significant decreases were seen from the first to the last investigation. Neither boys nor girls without proteinuria showed any changes in renal function during follow up.

Table 2 Renal haemodynamic data on the 38 patients investigated more than once (that is, 2–6 times). Results are mean (SEM) and for GFR and ERPF in ml/min/1·73 m^2

	First investigation	*Last investigation*
All patients (n=38)		
Time from onset (years)	3·2 (0·5)	7·8 (0·6)
GFR	114 (2)***	105 (4)§§§
ERPF	594 (16)**	542 (21)§§
Boys (n=22)		
Time from onset (years)	2·4 (0·5)	6·8 (0·7)
GFR	117 (3)**	106 (4)§§§
ERPF	607 (20)*	551 (25)§§
Girls (n=15)†		
Time from onset (years)	4·4 (0·8)‡	9·7 (1·0)‡
GFR	113 (3)§	109 (4)§§
ERPF	580 (26)	562 (21)§
Boys and girls with proteinuria (n=17)†		
GFR	115 (4)***	100 (4)§§§
ERPF	604 (26)***	519 (28)§§§
Boys and girls without proteinuria (n=20)		
GFR	116 (2)	114 (3)¶¶
ERPF	589 (19)	586 (17)¶
Boys with proteinuria (n=12)		
GFR	117 (5)***	97 (6)§§§
ERPF	616 (31)***	509 (36)§§§
Boys without proteinuria (n=10)		
GFR	118 (4)	116 (3)¶¶
ERPF	597 (24)	601 (27)
Girls with proteinuria (n=5)†		
GFR	111 (7)	105 (6)§§
ERPF	577 (53)	543 (48)§
Girls without proteinuria (n=10)		
GFR	114 (3)	111 (5)§
ERPF	581 (31)	571 (21)

†The girl with the nephrotic syndrome excluded.
‡Significantly ($p<0·05$) different from the boys.
*$p<0·05$, **$p<0·01$, ***$p<0·001$, difference between first and last investigation by paired *t* test.
§$p<0·05$, §§$p<0·01$, §§§$p<0·001$, significantly different from that of controls by paired *t* test.
¶$p<0:05$, ¶¶$p<0·01$, significantly different from those with proteinuria by paired *t* test.

Table 3 Last renal haemodynamic data on the patients with an initially raised serum creatinine concentration in comparison with those with normal serum creatinine concentrations at the onset. Results are mean (SEM)

	Raised creatinine at onset (n=15)	*Normal creatinine at onset (n=36)*
Duration of disease (years)	4·6 (1·0)*	7·2 (0·7)
GFR (ml/min/1·73 m^2)	98 (8)**	110 (2)
ERPF (ml/min/1·73 m^2)	538 (47)	580 (18)
Filtration fraction (%)	18·1 (0·7)	19·5 (0·5)

*$p<0·05$ and **$p<0·01$ indicate a significant difference between the groups.

Table 3 gives the last renal haemodynamic data on the 15 patients with increased serum creatinine values at the onset of the disease in comparison with the 36 patients who did not show raised serum creatinine concentrations in their first episode. Patients with signs of acute nephritic syndrome at the onset, that is, raised serum creatinine concentration with haematuria and/or proteinuria, seem to have a poorer prognosis, with a lower GFR despite a shorter follow up period.

Renal function in patients with macroscopic haematuria at the onset did not differ from those without macroscopic haematuria either at the first or last renal function investigations. Nor was there any difference in renal function at the first or last investigation in those with raised or normal serum IgA concentrations.

Discussion

There are few long term follow up studies of patients with a clinical onset of IgA nephropathy during childhood.[19 20 24 25] In adult as well as in most childhood studies there is a male preponderance,[2 3 12 14 16 25 26] although Kusumoto *et al* report a rather similar distribution between the sexes in juvenile in contrast to adult onset IgA nephropathy.[13] In the present study the ratio of males to females is about 1·5:1. Furthermore, the disease seems to present at an earlier age in girls than in boys. This has not been reported explicitly previously,[16 17] but it also seems to occur even in another report on childhood IgA nephropathy.[24] The question is whether or not the disease has an earlier onset in girls. As urinary tract infections are much more common in girls,[27] more urinalyses may be performed in them than in boys in connection with uncertain disorders and result in an earlier detection of asymptomatic patients among girls. This possibility is further supported by the fact that the presenting symptoms in girls are more often microscopic haematuria and proteinuria, while macroscopic haematuria is found significantly more often as the symptom of onset among boys. This higher frequency of macroscopic haematuria in males has also been found by others.[1 5 16] Futhermore, gross haematuria seems to occur much more often among children than among adults.[1 3 12 16 19 24] In the present study macroscopic haematuria did not seem to be related to a poorer prognosis as the last renal functional data did not differ between patients with or without macroscopic haematuria, as has also been found by others.[5 6 9 11 17] Australian studies found significantly worse renal function in adults with a history of macroscopic haematuria,[16 28] however, which was also found by Linné *et al* in juvenile onset IgA nephropathy.[20]

In this study raised serum IgA concentrations were found in 47% of the patients, which is in line with other reports.[13 17 23] Kher *et al*[3] and Michalk *et al*[19] found much lower frequencies and concluded that serum IgA did not appear to be a diagnostic test of IgA nephropathy in children.[3] This is in contradiction to Kusumoto, who found a similar frequency in children to that in adults, that is, about 35%.[13] Nor did they find any correlation between serum IgA concentration and the prognosis, which is well in line with the findings of the present study and other ones.[5–7 9 14 16] Droz, however, reported a more favourable outcome in patients with higher serum concentrations of IgA,[4] but in a later report he claimed that serum IgA concentrations had no prognostic significance.[17]

The rather high frequency of 29% of children with raised serum creatinine values at the onset is in good accord with the findings of other studies,[5 8 14 16 20] but this was not seen by Kher,[3] and in only a few cases by Lévy *et al.*[1] Hood *et al*[14] and Nicholls *et al*[16] found it more often in males, which was not found in the present study. This acute nephritic syndrome is usually reversible.[5 24] In the present study GFR returned to normal in two thirds of the patients during follow up, and in one third it progressed. Hood *et al* reported progression in about half of the patients and regression in the other half.[14] A long term follow up of renal function in these patients with raised serum creatinine at the onset showed a lower GFR in comparison with those with normal serum creatinine concentrations at the onset, and this finding is supported by Hood *et al.*[14]

In the initial renal functional data on the group of patients with raised serum creatinine values at the onset, the GFR, ERPF, and filtration fraction were significantly reduced. The low filtration fraction indicates a more reduced GFR than ERPF, which might support the hypothesis of relative hyperperfusion of a reduced number of functioning nephrons. The tendency of a relative hyperperfusion seems to remain during the first four years of the disease, after which time the ERPF goes down as well. Very few studies on renal function have been made with a special emphasis on determinations of renal plasma flow. Linné *et al* found supernormal GFRs (>+1 SD of those of controls) in seven out of 15 patients studied five to 17 years after the onset, but clearance of para-aminohippuric acid was within normal limits.[20]

As in other studies,[1 4–6 15] the nephrotic syndrome at clinical presentation was an infrequent finding. The prognosis in patients with heavy proteinuria seemed to be worse, however. This was also the case with the girl with the nephrotic syndrome in this study, who was the only one whose disease progressed to terminal renal failure within the short period of 2·6 years. The fact that proteinuria is associated with a poor prognosis is shown in this study as in other ones.[5 9 10 11 14–17 24] Chida *et al* found a significant decrease in the renal survival rate in patients with proteinuria of more than 1 g/day and the most unfavourable prognosis in those with heavy proteinuria.[11] Clarkson *et al* point out that progressive disease becomes more manifest in the older proteinuric patients.[5] In another study, where we explicitly examined renal function in relation to urine protein excretion, without the aspect of long term follow up, we found that patients with microalbuminuria had a reduced GFR, indicating that even microalbuminuria is a marker of progressive disease.[29]

The present results also show that male gender is more frequently correlated with deterioration of renal function, as has been demonstrated by others.[10 14 16 17 24] Droz found no differences between the sexes.[4] In the present study girls with proteinuria had a decreased GFR and ERPF at the last renal function investigation, but they did not show a significant decrease from the first to the last examination. This might be due to the rather low number of girls with proteinuria studied. Girls have been reported to have a higher incidence of mild glomerular changes,[24] but that study did not demonstrate any difference between the sexes in GFR, proteinuria, and the incidence of hypertension, that is, in the clinical outcome. The follow up time was rather brief, however, with a mean of 3 years 4 months.

In summary several earlier reports have stressed the benign clinical course of IgA nephropathy with an onset of disease during childhood, but this long term follow up study of renal function has shown that children with IgA nephropathy and proteinuria, especially boys, have a poor prognosis. Patients with raised serum creatinine concentrations at the onset also seem to develop renal dysfunction as well as do the few children with hypertension in connection with IgA nephropathy.

The study was supported by grants from the Karolinska Institute and the Swedish Medical Research Council (No/6864).

1 Lévy M, Beaufils H, Gubler MC, Habib R. Idiopathic recurrent macroscopic hematuria and mesangial IgA-IgG deposits in children (Berger's disease). *Clin Nephrol* 1973;1:63–9.
2 McCoy RC, Abramowsky CR, Tisher CC. IgA nephropathy. *Am J Pathol* 1974;76:123–44.
3 Kher KK, Makker SP, Moorthy B. IgA nephropathy (Berger's disease)—a clinicopathologic study in children. *Int J Pediatr Nephrol* 1983;4:11–8.
4 Droz D. Natural history of primary glomerulonephritis with mesangial deposits of IgA. *Contrib Nephrol* 1976;2:150–7.
5 Clarkson AR, Seymour AE, Thompson AJ, Haynes WDG, Chan YL, Jackson B. IgA nephropathy: a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol* 1977;8:459–71.
6 van der Peet J, Arisz L, Brentjens JRH, Marrink J, Hoedemaeker PJ. The clinical course of IgA nephropathy in adults. *Clin Nephrol* 1977;8:335–40.
7 d'Amico G, Ferrario F, Colasanti IG, Ragni A, Bosisio MB.

IgA mesangial nephropathy (Berger's disease) with rapid in renal function. *Clin Nephrol* 1981;**16**:251–7.

8 Lee SMK, Rao VM, Franklin WA, *et al.* IgA nephropathy: morphologic predictors of progressive renal disease. *Hum Pathol* 1982;**13**:314–22.

9 Kobayashi Y, Tateno S, Hiki Y, Shigematsu H. IgA nephropathy: prognostic significance of proteinuria and histological alterations. *Nephron* 1983;**34**:146–53.

10 Rambausek M, Seelig HP, Andrassy K, *et al.* Mesangiale IgA Glomerulonephritis. Neue Aspekte zur Diagnose, Klinik und Prognose. *Dtsch Med Wochenschr* 1983;**108**:125–30.

11 Chida Y, Tomura S. Takeuchi J. Renal survival rate of IgA nephropathy. *Nephron* 1985;**40**:189–94.

12 Mina SN, Murphy WM. IgA nephropathy. A comparative study of the clinicopathologic features in children and adults. *Am J Clin Pathol* 1985;**83**:669–75.

13 Kusumoto Y, Takebayashi S, Taguchi T, Harada T, Naito S. Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and in adult Japanese. *Clin Nephrol* 1987; **28**:118–24.

14 Hood SA, Velosa JA, Holley KE, Donadio JV. IgA-IgG nephropathy: predictive indices of progressive disease. *Clin Nephrol* 1981;**16**:55–62.

15 Katz A, Walker JF, Landy PJ. IgA nephritis with nephrotic range proteinuria. *Clin Nephrol* 1983;**20**:67–71.

16 Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P. The clinical course of mesangial IgA associated nephropathy in adults. *Q J Med* 1984;**210**:227–50.

17 Droz D, Kramar A, Nawar T, Noel LH. Primary IgA nephropathy: prognostic factors. *Contrib Nephrol* 1984;**40**: 202–7.

18 Roy LP, Fish AJ, Vernier RL, Michael AF. Recurrent macroscopic hematuria, focal nephritis, and mesangial deposition of immunoglobulin and complement. *J Pediatr* 1973;**82**:767–72.

19 Michalk D, Waldherr R, Seelig HP, Weber HP, Schärer K. Idiopathic mesangial IgA-glomerulonephritis in childhood. *Eur J Pediatr* 1980;**134**:13–22.

20 Linné T, Aperia A, Broberger O, Bergstrand A, Bohman SO, Rekola S. Course of renal function in IgA glomerulonephritis in children and adolescents. *Acta Paediatr Scand* 1982; **71**:735–43.

21 Berg U, Bohlin AB. Renal hemodynamics in minimal change nephrotic syndrome in childhood. *Int J Pediatr Nephrol* 1982;**3**:187–92.

22 Hilger HH, Klumper JD, Ullrich KJ. Wasserrückresorption und Ionentransport durch die Sammelrohrzellen der Saügetierniere. *Pflugers Arch* 1958;**267**:218–37.

23 Smith HW, Fingelstein N, Aliminosa L, Crawford B, Graber M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dogs and man. *J Clin Invest* 1945;**24**:338–404.

24 Hogg RJ, Silva F. A multicenter study of IgA nephropathy in children. A report of the Southwest pediatric nephropathy study group. *Kidney Int* 1982;**22**:643–52.

25 Lévy M, Gonzalez-Burchard G, Broyer M, *et al.* Berger's disease in children. Natural history and outcome. *Medicine* 1985;**64**:157–80.

26 Clarkson AR, Woodroffe AJ, Bannister KM, Lomax-Smith JD, Aarons I. The syndrome of IgA nephropathy. *Clin Nephrol* 1984;**21**:7–14.

27 Winberg J, Bergström T, Jacobsson B. Morbidity, age and sex distribution, recurrences and renal scarring in symptomatic urinary tract infection in childhood. *Kidney Int* 1975;**8**:S101–6.

28 Bennett WM, Kincaid-Smith P. Macroscopic hematuria in mesangial IgA nephropathy: correlation with glomerular crescents and renal dysfunction. *Kidney Int* 1983;**23**: 393–400.

29 Widstam-Attorps UC, Berg UB. Urinary protein excretion and renal function in children with IgA-nephropathy. *Pediatric Nephrology* 1991 (in press).

INSTITUTE OF CHILD HEALTH
(University of London)

Advanced Paediatric Neurology:
Infections and the Nervous System

10–12 June 1991

This course will focus on recent advances in infections of the nervous system in the paediatric age group. It will include contributions on epidemiology, pathology, clinical and laboratory aspects. It is intended for Paediatric Neurologists.

Fee: £165·00 (including lunch and refreshments).

For full programme and registration form please contact:

Short Courses Office
Institute of Child Health
30 Guilford Street
London
WC1N 1EH
Tel: 071–829 8692

Calculate with confidence:

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton, the IBM compatible program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- non-parametric analyses

For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program (available on 5¼" or 3½" disk) may also be used in conjunction with the book **Statistics with Confidence*, which provides numerous worked examples.

£65.00. Educational establishments, research institutes, and the NHS —£45.95. Prices include VAT in the UK and air mail despatch abroad

★*UK £7.95; Abroad £9.50*
BMA members UK £7.45; Abroad £9.00
Please enclose payment with order (stating size of disk required), or send us full details of your MASTERCARD, VISA or AMERICAN EXPRESS credit card.

Order from: BRITISH MEDICAL JOURNAL
PO Box 295, London WC1H 9TE

CURRENT PAEDIATRICS

New from
Churchill Livingstone
First issue now available

Chairman *D Hull*
Executive Editor *R Wilson*
Editorial Committee *M Dillon, D Hall and M Levene*

Current Paediatrics will provide busy clinicians with educational reviews designed to keep them up to date in paediatrics and child health. Over a 3-year cycle of 12 quarterly issues, the journal will cover most of the relevant topics. The emphasis of the journal will be on clear, concise presentations of information of direct clinical relevance to both hospital and community-based paediatricians.

Current Paediatrics will be invaluable to MRCP and DCH candidates *as well as for* fully qualified paediatricians.

Current Paediatrics will keep you up to date on delivery of care, technical procedures, investigations, innovations, legal matters and basic science.

The first issue includes...
Diagnosis and management of the acute abdomen, Management of chronic constipation, Vomiting, Acute upper airway obstruction, Chronic upper airway obstruction, The management of asthma, Occult lesions of the spine, Post neonatal infant mortality, Prophylaxis of meningitis in childhood, Physiotherapy in neurological disorders, Measurement of intracranial pressure, Making health education work.

Subscription Information
ISSN 0957-5839 Volume 1 First issue March 1991

Trainee	UK £25.00	USA $46.50	Other £29.00
Individual	UK £35.00	USA $65.00	Other £40.00
Insitutional	UK £89.00	USA $164.00	Other £102.50

If you would like a **free sample copy** of the first issue or would like to subscribe, please write to
Sales Promotion Department
Churchill Livingstone Medical Journals
Robert Stevenson House, Baxter's Place,
Edinburgh EH1 3AF, UK

Churchill Livingstone

MONATSSCHRIFT KINDERHEILKUNDE

139. Band Heft 3
März 1991

Organ der
Deutschen Gesellschaft
für Kinderheilkunde

Thema des Monats

Mukopolysaccharidosen
Editorial 119

M. Beck
Mukopolysaccharidosen: Nosologie – Klinik – Therapieansätze 120

Pädiatrie aktuell

Enterokokken als Sepsisursache bei Neu- und Frühgeborenen

Senkt die bereits vor der Schwangerschaft einsetzende Verbesserung der Stoffwechseleinstellung insulinabhängiger Diabetikerinnen das Risiko der Geburt fehlgebildeter Kinder?

Vergleich unterschiedlicher Immunglobulindosen bei der Behandlung des Kawasaki-Syndroms 128

Was hat das Kind?

Trainingsprogramm für die Weiterbildung zum Kinderarzt 129

Klinik und Forschung

S. Liptay, C. P. Bauer, A. Grübl, R. Franz, P. Emmrich
Atopieentwicklung in der frühen Kindheit – Prädisponierende Faktoren 130

Ch. Pabelick, B. Koletzko
Befunde bei Neugeborenen nierentransplantierter Mütter 136

W. Klapsch, Ch. Tschauner, R. Graf
Kostendämpfung durch die generelle sonographische Hüftvorsorgeuntersuchung 141

H. Bode, R. Bubl
Hirndurchblutung bei zerebralen Residualschäden. Eine Doppler-sonographische Studie 144

Der interessante Fall

U. Bertram, G. Hüls, W. Padberg, J. Turski, M. Altmannsberger
Entzündlich fibroider Polyp des Magens als ungewöhnliche Differentialdiagnose eines Oberbauchtumors 151

I. D. Mutz, R. Stering
Konnatales Neuroblastom und Plazentametastasen 154

W. Sperl, H. Fischer, J. Hager
Chilaiditi's Koloninterposition bei einer Patientin mit Rett-Syndrom 157

B. Sommer, H. L. Spohr
GM_2-Gangliosidose Variante 0 (M. Sandhoff): Verdachtsdiagnose einer Speicherkrankheit durch Ultraschall 160

Wußten Sie schon?

Aus der Klinik – für die Klinik

G. Conrad, A. Ch. Ludwig, F. Daschner
Sinnvolle und umweltschonende Desinfektion in der Pädiatrie 163

G. Conrad, M. Scherrer, F. Daschner
Vorschläge zur Abfallvermeidung und Umweltschutz in der Kinderklinik und kinderärztlichen Praxis 168

Was hat das Kind?

Auflösung und Kommentar des Trainingsprogramms 156

Tagesgeschichte 170
Tagungskalender 170

Abstracts der 21. Jahrestagung der Arbeitsgemeinschaft für Pädiatrische Nephrologie, 7.–9. 3. 1991 in Essen 174

Abstracts der 6. Jahrestagung der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung, 1.–4. 5. 1991 in Goldegg 189

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Hong Kong Barcelona Budapest

Annual subscription: DM 298,- plus postage

Archives of Disease in Childhood 1991; 66: 593–597

Renal histological changes in relation to renal function and urinary protein excretion in IgA nephropathy

U B Berg, S–O Bohman, U Widstam-Attorps

Karolinska Institute, Huddinge University Hospital, Sweden, Department of Paediatrics
U B Berg

Department of Pathology
S–O Bohman

Department of Renal Medicine
U Widstam-Attorps

Correspondence to:
Dr U Widstam-Attorps,
Department of
Renal Medicine,
Huddinge University
Hospital,
S-141 86 Huddinge,
Sweden.

Accepted 30 November 1990

Abstract

Renal function and urinary protein excretion (UPE) were investigated at the time of kidney biopsy in 24 children with IgA nephropathy. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by clearances of inulin and para-aminohippuric acid. For UPE albumin, IgG, β_2 microglobulin, and creatinine were analysed. Glomerular global/segmental sclerosis and crescents in the biopsy specimens were assessed, and glomerular and tubulointerstitial changes classified on a five degree scale.

The patients with tubulointerstitial or mesangial biopsy changes or glomerular sclerosis had significantly lower GFR than those without corresponding lesions. Patients with segmental sclerosis also had higher excretion rates of IgG, which increased with increasing segmental sclerosis. Six patients had GFRs below 2SD of the controls. Within the group of patients with reduced GFR overt albuminuria, a raised excretion rate of IgG, interstitial fibrosis, and advanced mesangial lesions were more frequent. A rising excretion rate of IgG seems to indicate both reduced GFR and increasing segmental glomerulosclerosis and may be a marker of progressive disease.

Since the first report in 1968 by Berger and Hinglais[1] IgA nephropathy has become recognised as a common form of chronic glomerulonephritis.[2 3] The growing awareness that IgA nephropathy is a progressive kidney disease in a certain percentage of cases leading to end stage renal failure has inspired a search for prognostic markers.[4–7] Glomerular sclerosis and interstitial fibrosis are histological features associated with an increased risk of developing renal failure.[2 6 8 9] An older age at the onset of the disease, heavy proteinuria, hypertension, and male gender are clinical predictors of a poorer prognosis.[2 4 8–11] IgA nephropathy may also lead to uraemia in childhood.[12–14] This study was designed to characterise the morphological changes in kidney biopsy specimens from children and adolescents with IgA nephropathy, and to correlate the findings with the pattern of urinary protein excretion (UPE) as well as with renal haemodynamics at the time of the kidney biopsy, and to evaluate the diagnostic and prognostic significance of UPE and renal haemodynamics.

Patients and methods

UPE and renal haemodynamics were studied in 24 children and adolescents (16 boys, eight girls) with IgA nephropathy within 34 days of a kidney biopsy, mean (SEM) 2·8 (1·4) days. The mean (SEM) age of the patients was 13·3 (0·7) years and the investigations were performed 0·13–12·3 (mean 3·9 (0·7)) years after the first signs or symptoms of kidney disease. The patients were all in a stable condition without signs of current infection.

Renal biopsies were performed percutaneously using a Tru-Cut biopsy needle having an outer diameter of 2·0 mm (Travenol). Tissue for light microscopy was fixed in 3% buffered formaldehyde, and embedded in paraffin. Two to 3 micron thick sections were stained with haematoxylin and eosin, Ladewigs trichrome stain, and silver methenamine. Tissue for immunofluorescence microscopy was frozen immediately in liquid nitrogen. Unfixed frozen sections were incubated with fluorescein isothiocyanate (FITC)-conjugated antisera (Dako) against human IgG, IgM, IgA, C3, and C1q.

All biopsy specimens were examined without knowledge of other laboratory data or patient histories. The percentage of glomeruli showing global sclerosis, segmental sclerosis, and cellular crescents was calculated. A number of glomerular and tubulointerstitial parameters were then assessed semiquantitatively on a five degree scale (0, ±, +, ++, +++). These included glomerular mesangial expansion, mesangial cell proliferation, interstitial fibrosis and tubular atrophy, interstitial inflammation, and vascular lesions.

Urine analyses for UPE were based on timed short term collections, and blood was drawn in connection with the sampling period. Albumin, IgG, β_2 microglobulin, and creatinine were measured in serum and urine, and the respective excretion rates, clearances, and fractional clearances were calculated.

Renal function was determined as the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) and measured as clearances of inulin and para-aminohippuric acid during water diuresis using a standard clearance technique.[15] This includes a priming dose and continuous infusion of inulin and para-aminohippuric acid. The filtration fraction and fractional sodium excretion were also determined.

Serum albumin was analysed by an automated dye binding method with bromcresol purple[16]; urinary albumin and IgG, and serum IgG were analysed by an automated immunonephelometric method (Behring Nephelometer Analyser). β_2 Microglobulin was assayed by a radioimmunological method (Phadebas, β2-micro Test, Pharmacia Diagnostics AB). Creatinine was determined by a kinetic method based on a modified Jaffé reaction,[17] and serum sodium with ion selective electrodes and urinary sodium by flame photometry. Inulin was analysed by the anthrone method[18] and para-aminohippuric acid by a modified Smith technique.[19]

To evaluate the distribution of proteinuria, the patients' urines were screened by the routine laboratory detection limits for the different proteins (albumin $\geqslant$30 mg/l, IgG $\geqslant$10 mg/l, β_2 microglobulin $\geqslant$100 µg/l). For statistical analyses the patients were grouped according to the type and extent of morphological changes in the biopsy specimen and according to the urinary excretion rates of the respective proteins: (1) urinary excretion rate of albumin <20 µg/min/1·73 m^2 (or urinary albumin <30 mg/l) (non-albuminuria), 20–200 µg/min/1·73 m^2 (microalbuminuria) and >200 µg/min/1·73 m^2 (albuminuria); (2) urinary excretion rate of IgG <10 and $\geqslant$10 µg/min/1·73 m^2, and (3) urinary excretion rate of β_2 microglobulin <200 and $\geqslant$200 ng/min/1·73 m^2.

The results in the different groups were expressed as the mean (SEM) and were compared by means of the Mann-Whitney non-parametric test. The χ^2 test was peformed for associations of categorical variables, and the correlation between variables was assessed by linear regression analysis. Thirty six healthy children and adolescents without any signs of kidney disease (mean age 12·8 (0·9) years, range 3·5–21·5 years) served as controls regarding renal haemodynamics.

Results

By definition, all biopsy specimens included in this study showed a positive immunofluorescence reaction in the glomeruli with IgA as the predominant immunoglobulin, which mainly occurred in the mesangial areas. In the vast majority of cases (92%) C3 was present in a similar pattern while C1q was usually negative. No patient showed any evidence of systemic disease associated with glomerular IgA deposits.

The distribution of the patients according to tubulointerstitial and glomerular changes is given in table 1. No biopsy specimen showed significant arteriolosclerosis. Thirteen of the 24 patients (54%) had glomerular sclerosis or crescent formations: nine exhibited glomeruli with global sclerosis (up to 10% glomeruli affected), eight segmental sclerosis (up to 19% glomeruli affected), and two had focal crescent formations.

There were no significant differences in UPE when the patients were grouped according to mesangial changes (volume expansion and cell proliferation). The patients with modest/moderate (+/++) mesangial changes (volume expansion as well as cell proliferation) had a lower GFR than those with no mesangial alterations (table 2). Mesangial volume expansion associated significantly with mesangial cell proliferation (fig 1). The duration of the IgA nephropathy was not longer in the four patients with mesangial volume expansion predominating over mesangial cell proliferation.

The patients with glomerular sclerosis (global as well as segmental) had significantly lower GFR than those without corresponding glomerular changes (fig 2). The patients with segmental sclerosis also had higher urinary excretion rates of IgG (55·1 (13·4) µg/min/1·73 m^2, $p<0{\cdot}05$), higher IgG clearance, higher fractional IgG clearance, and higher serum β_2 microglobulin concentrations (2·5 (0·4) mmol/l, $p<0{\cdot}01$) compared with the patients with no segmental sclerosis (IgG excretion rate 14·8 (5·0) µg/min/1·73 m^2 and serum β_2 microglobulin 1·3 (0·1) mmol/l). There were highly significant correlations between the proportions

Table 1 Distribution of the patients according to the extent (semiquantitative score) of tubulointerstitial and glomerular mesangial damage

Score	Interstitial fibrosis	Interstitial inflammation	Mesangial expansion	Mesangial cell proliferation
0	13	20	6	8
±	8	1	8	7
+	3	3	7	7
++	0	0	3	2
+++	0	0	0	0

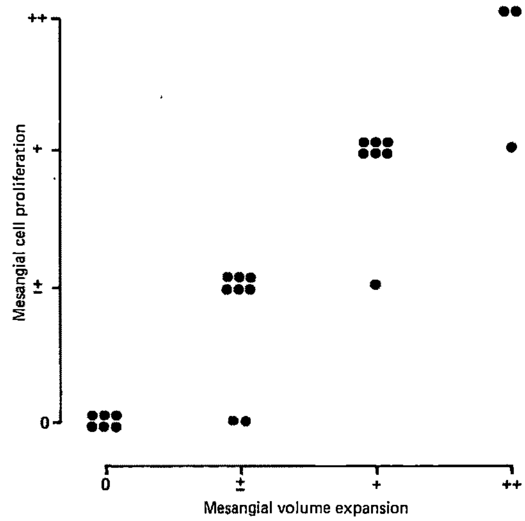


Figure 1 Correlation between the extent of mesangial cell proliferation and mesangial volume expansion (semiquantitative score).

Table 2 Mean (SEM) GFR ml/min/1·73 m^2 in the patients grouped according to extent (semiquantitative score) of glomerular mesangial and tubulointerstitial biopsy findings

Group	Extent of mesangial and interstitial changes		
	0 [n]	± [n]	+/++ [n]
Measangial volume expansion	122 (6) [6]	113 (5) [8]	100 (7) [10]*
Measangial cell proliferation	118 (5) [8]	119 (6) [7]	96 (7) [9]*†
Interstitial fibrosis	119 (4) [13]	105 (5) [8]*	76 (12) [3]**
Interstitial inflammation	115 (3) [20]‡	64 [1]	90 (17) [3]

*$p<0{\cdot}05$ compared with 0, **$p<0{\cdot}01$ compared with 0, †$p<0{\cdot}05$ compared with ±, ‡$p<0{\cdot}05$ compared with ±/+/++.

Table 3 Coefficients of correlation (r) between the extent of glomerular sclerosis and excretion rates, clearances, and fractional clearances of albumin and IgG respectively

	Segmental sclerosis (%)	*Segmental and global sclerosis (%)*	*Global sclerosis (%)*
Albumin excretion rate	0·80***	0·86***	0·59
IgG excretion rate	0·87***	0·84***	0·44
Albumin clearance	0·78***	0·88***	0·67**
IgG clearance	0·88***	0·90***	0·58*
Albumin clearance/inulin clearance	0·72**	0·85***	0·71**
IgG clearance/inulin clearance	0·83***	0·90***	0·68*

*$p<0\cdot05$, **$p<0\cdot01$, ***$p<0\cdot001$.

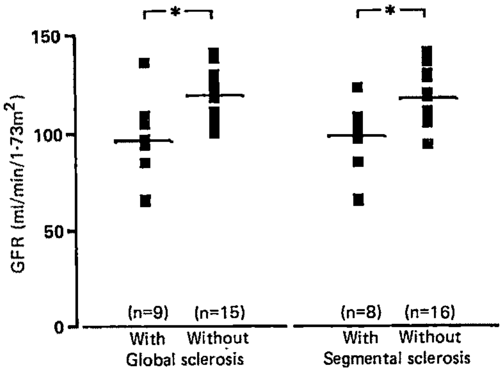


Figure 2 GFR in patients grouped according to the presence of global and segmental glomerular sclerosis respectively; $p<0\cdot05$.

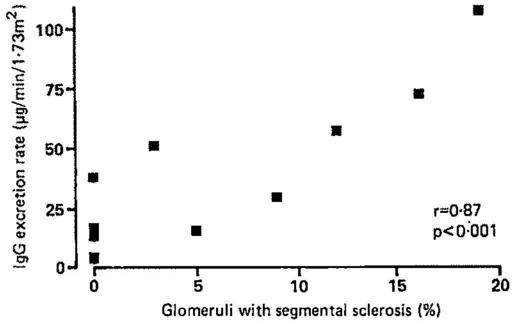


Figure 3 Correlation between the IgG excretion rate and the percentage of glomeruli with segmental sclerosis.

of sclerotic glomeruli and urinary excretion of albumin and IgG, which is illustrated in table 3 and fig 3.

The patients with tubulointerstitial changes in the biopsy specimen (fibrosis and/or inflammation), had a lower GFR than those with no interstitial changes. GFR (table 2) and ERPF declined with advancing fibrosis, while fractional sodium excretion increased. Fractional sodium excretion was significantly higher (2·03 (0·22)%, $p<0\cdot05$) in patients with modest (+) interstitial fibrosis than in those with no (1·22 (0·10)%) or slight (±, 1·31 (0·17)%) fibrosis. There were no significant differences in UPE between the interstitial groups.

Sixteen of the 24 patients (67%) had urinary albumin >30 mg/l (mean 684 (433) mg/l), five patients (21%) were Albustix positive (urinary albumin >150 mg/l, mean 2040 (1256) mg/l), and three (9%) were nephrotic with urinary excretion rates of albumin of >40 mg/h/m^2, mean 3072 (1974) mg/l). Twelve patients (50%) had urinary IgG >10 mg/l (mean 59·8 (31·2) mg/l), and nine patients (39%) had urinary β_2 microglobulin of >100 μg/l (mean 200 (41) μg/l). Only one patient had a urinary β_2 microglobulin concentration above the upper reference limits (<375 μg/l).

The mean GFR (110 (4) ml/min/1·73 m^2) and ERPF (571 (24) ml/min/1·73 m^2) in the patient group were significantly reduced compared with controls (119 (2) and 627 (14) ml/min/1·73 m^2 respectively, $p<0\cdot05$) but the filtration fraction did not discriminate (19·5 (0·7)% and 19·2 (0·4)% respectively).

No patient was hypertensive (mean systolic blood pressure 114 (2), diastolic 67 (2) mm Hg), but one boy with albuminuria and a reduced GFR was on antihypertensive treatment.

The albumin excretion rate was determined in 23 patients (one girl missed the urine collection). GFR in those without albuminuria (124 (5) ml/min/1·73 m^2) did not differ from controls, but those with microalbuminuria (104 (6) ml/min/1·73 m^2) and with albuminuria (95 (9) ml/min/1·73 m^2) had significantly ($p<0\cdot05$) lower GFRs compared with non-albuminurics as well as with controls. The urinary excretion rate of IgG increased with rising urinary albumin excretion rate. The blood pressure tended to rise with increasing albumin excretion, and the albuminuric patients (mean blood pressure 118 (5)/74 (2) had significantly higher diastolic blood pressure ($p<0\cdot05$) than the non-albuminurics (mean blood pressure 109 (3)/65 (3)).

The patients with rates of urinary excretion of IgG >10 μg/min/1·73 m^2 had a lower GFR (95 (6) ml/min/1·73 m^2, $p<0\cdot01$) than those with excretion rates <10 μg/min/1·73 m^2 (119 (4) ml/min/1·73 m^2) but there were no further significant differences in renal haemodynamics or UPE between the two groups, nor in the groups based on excretion rates of β_2 microglobulin.

Six patients had GFRs below 2SD of the controls (<100 ml/min/1·73 m^2). A comparison of this group of patients using the χ^2 test to those with GFR >100 ml/min/1·73 m^2 revealed significantly more patients with overt albuminuria (4/6, $p<0\cdot05$) and raised urinary excretion rates of IgG (6/6, $p<0\cdot01$) and more patients with interstitial fibrosis (6/6, $p<0\cdot01$), >± mesangial cell proliferation (6/6, $p<0\cdot05$), >± mesangial volume expansion (5/6, $p>0\cdot05$), and more global sclerosis (5/6, $p<0\cdot05$).

One patient (a 13 year old boy) developed end stage renal failure within seven months of the kidney biopsy, which had demonstrated a slight mesangial volume expansion and cell proliferation, slight interstitial fibrosis, 19% glomeruli with segmental and 10% with global sclerosis. At the time of biopsy he was nephrotic with a reduced GFR (93 ml/min/1·73 m^2) and ERPF (466 ml/min/1·73 m^2).

Discussion

Although far from negligible, the morphological lesions of our patients were less prominent than those generally described in studies of adult IgA nephropathy patients.[2 3 20] Still the mean GFR and ERPF values at the time of biopsy were significantly lower than in controls, and one fourth of the patients exhibited a reduced GFR (below 2SD). Thus the severity of an IgA nephropathy, even in childhood, must not be underestimated.

Many investigations have been made to evaluate clinical factors predicting progressive renal disease in IgA nephropathy.[8 10] The type of glomerular lesions observed in the first renal biopsy in childhood IgA nephropathy has been claimed to be predictive of the clinical course of the disease.[13 11] Already at the time of biopsy our patients with more advanced morphological lesions (glomerular and/or tubulointerstitial) had lower GFRs than those with no or less pronounced changes in their biopsy specimens.

Mesangial volume expansion and mesangial cell proliferation coincided except in four cases with more pronounced mesangial expansion than cell proliferation (fig 1). These results differ somewhat from those of Yoshikawa *et al* who found predominant mesangial hypercellularity to be characteristic of early childhood IgA nephropathy, while the mesangial matrix increased later, suggesting progressive disease.[21 22] Their children with prominent hypercellularity had the shortest interval between onset of the disease and biopsy (mean (SD) 4·1 (4·0) months). All Japanese schoolchildren are screened yearly for urinary abnormalities and renal diseases are therefore often diagnosed at an early age in Japan. Our biopsies were performed with a median interval of 2·6 years from onset of disease, thus corresponding to the children studied by Yoshikawa *et al* with waning hypercellularity. Consequently the difference in our results mainly consists in our findings of persisting mesangial cell proliferation.

Half of our patients (54%) exhibited sclerotic glomeruli, and these patients had reduced renal function and higher IgG excretion, though no patient had more than 19% glomeruli with segmental sclerosis. These findings agree with the assumption that glomerular obsolescence and segmental glomerulosclerosis are associated with an increased risk of renal failure.[2 3 5–9] Vascular lesions are unusual in children,[12 22] and we recorded no vascular changes. Thus the glomerular sclerosis could not be attributed to ischaemic damage,[2 23] which also agrees with previous findings by D'Amico *et al.*[9]

Interstitial lesions, especially interstitial fibrosis, have been claimed to be associated with an increased risk of developing renal failure.[2 8] Although interstitial findings were sparse, the patients with interstitial changes had reduced GFR. The fact that interstitial lesions did not correlate with the extent of glomerular changes suggest that at least partly different mechanisms are responsible for glomerular and tubulointerstitial damage, which has also been observed previously by D'Amico *et al.*[9]

Heavy proteinuria is another marker of severe disease.[4 5 6 8 9] The reduced GFRs found in albuminuric as well as in microalbuminuric patients correspond to our previous findings[24] that microalbuminuria may also be a marker of more severe IgA nephropathy.[24] A rising IgG excretion rate seems to indicate both a reduced GFR and increasing segmental glomerulosclerosis. As the extent of segmental sclerosis is considered to be associated with an increased risk of developing renal failure,[9] raised IgG excretion may be predictive of progressive renal disease.

GFR was reduced in patients with comparatively modest mesangial, sclerotic, or interstitial changes and deteriorated further with more severe histological damage. An exact GFR determination is therefore of great importance in the follow up of IgA nephropathy. Although GFR was reduced even in patients with minor morphological changes, urinary albumin and IgG excretions distinguished the patients with more advanced renal damage and mainly sclerotic glomerular lesions.

In summary, our patients with reduced renal function and raised albumin and IgG excretions had more pronounced histological renal lesions. We suggest that an accurate determination of renal haemodynamics and UPE at the time of biopsy may give an indication of the extent of renal damage. The fact that the IgG excretion rate increased in the patients with more extensive segmental glomerular sclerosis may make it a valuable analysis in the follow up of IgA nephropathy. Increasing IgG excretion may be an early marker of progressive disease.

This study was supported by grants from the Karolinska Institute and the Swedish Medical Research Council (Nos 5937 and 6864).

1 Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG. *Journal d' Urologie et de Nephrologie* 1968;**74**:694–5.

2 Clarkson AR, Seymour AE, Thompson AJ, Haynes WDG, Chan Y-L, Jackson B. IgA nephropathy: a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol* 1977;**8**:459–71.

3 D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. *Q J Med* 1987;**64**:709–27.

4 Chida Y, Tomura S, Takeuchi J. Renal survival rate of IgA nephropathy. *Nephron* 1985;**40**:189–94.

5 Imbasciati E, Colasanti G, Barbiano di Belgioioso G, *et al.* Long-term follow-up of IgA mesangial deposits glomerulonephritis. *Dialysis and Transplantation* 1977;**14**: 472–7.

6 Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P. The clinical course of mesangial IgA associated nephropathy in adults. *Q J Med* 1984;**53**:227–50.

7 Rambausek M, Seelig HP, Andrassy K, *et al.* Measangiale IgA Glomerulonephritis. Neue Aspekte zur Diagnose, Klinik und Prognose. *Dtsch Med Wochenschr* 1983;**108**: 125–30.

8 Kobayashi Y, Tateno S, Hiki Y, Shigematsu H. IgA nephropathy: prognostic significance of proteinuria and histological alterations. *Nephron* 1983;**34**:146–53.

9 D'Amico G, Minetti L, Ponticelli C, *et al.* Prognostic indicators in idiopathic IgA mesangial nephropathy. *Q J Med* 1986;**59**:363–78.

10 Hood SA, Velosa JA, Holley KE, Donadio Jr JV. IgA-IgG nephropathy: predictive indices of progressive disease. *Clin Nephrol* 1981;**16**:55–62.

11 Kusumoto Y, Takebayashi S, Taguchi T, Harada T, Naito S. Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and in adult Japanese. *Clin Nephrol* 1987; **28**:118–24.

12 Hogg RV, Silva F. A multicenter study of IgA nephropathy in children. A report of the Southwest pediatric nephrology study group. *Kidney Int* 1982;**22**:643–52.

13 Lévy M, Gonzalez-Burchard G, Broyer M, *et al.* Berger's disease in children. Natural history and outcome. *Medicine* 1985;**64**:157–80.

14 Mina SN, Murphy WM. IgA nephropathy. A comparative study of the clinicopathologic features in children and adults. *Am J Clin Pathol* 1985;**83**:669–75.

15 Berg U, Bohlin A-B. Renal hemodynamics in minimal change

nephrotic syndrome in childhood. *Int J Pediatr Nephrol* 1982;3:187–92.

16 Pinnell AE, Northam BE. New automated dye-binding method for serum albumin determination with bromcresol purple. *Clin Chem* 1978;**24**:80–6.

17 Masson P, Ohlsson P, Björkhem I. Combined enzymic-Jaffé method for determination of creatinine in serum. *Clin Chem* 1981;**27**:18–21.

18 Hilger HH, Klümper JD, Ullrich KJ. Wasserrückresorption und Ionentransport durch die Sammelrohrzellen der Säugetiernieren. *Pflugers Arch* 1958;**267**:218–37.

19 Smith HW, Fingelstein N, Aliminosa L, Crawford B, Graber M. The renal clearances of substituted hippuric acid derivates and other aromatic acids in dog and man. *J Clin Invest* 1945;**24**:388–404.

20 Croker BP, Dawson DV, Sanfilippo F. IgA Nephropathy. Correlation of clinical and histologic features. *Lab Invest* 1983;**48**:19–24.

21 Yoshikawa N, Iijima K, Matsuyama S, *et al.* Repeat renal biopsy in children with IgA nephropathy. *Clin Nephrol* 1990;**33**:160–7.

22 Yoshikawa N, Iijima K, Maehara K, *et al.* Mesangial changes in IgA nephropathy in children. *Kidney Int* 1987;**32**:585–9.

23 Feiner HD, Cabili S, Baldwin DS, Schacht RG, Gallo GR. Intrarenal vascular sclerosis in IgA nephropathy. *Clin Nephrol* 1982;**18**:183–92.

24 Widstam-Attorps U, Berg U. Urinary protein excretion and renal function in children with IgA-nephropathy. *Pediatric Nephrology* 1991 (in press).

Early diet and eczema

The association between early feeding and the later development of atopic diseases is a hardy perennial of a topic which has generated many an article but so far little of real practical importance. The role of breast feeding in this respect is still not clear. In a recent study from New Zealand, Ferguson and his colleagues (*Pediatrics* 1990;**86**:541–6) have examined the association between early solid feeding and later eczema.

They collected data on a cohort of 1265 children born in Christchurch in 1977 who were seen at birth, at 4 months, and at annual intervals to the age of 10 years. At the 4 month visit the amount and types of solid food given to the child were recorded, the foods being classified into six types: dairy products, egg or related products, cereals, vegetables, meat products, and fruit.

This report concerns the incidence of recurrent or chronic eczema. The diagnosis was accepted from the mother's report provided that the child had seen the family doctor at least three times for eczema, the condition had been present for at least three consecutive years, and the child was receiving regular treatment for eczema.

The overall incidence of recurrent or chronic eczema by the age of 10 years was 7·5%. The association between individual components of the early diet and later eczema was weak and not statistically significant. In comparison with those who had been given no solids up to the age of 4 months the risk of later eczema was increased by a factor of 2·35 in those who had received four or more types of food and by 1·4 in those who had received between one and three types. The findings were still significant after allowing for possible confounding variables such as family atopy, early breast feeding, or social background.

The authors therefore conclude that the development of eczema is related to the diversity of early diet rather than to individual dietary components.

Presumably for each individual child there may be a small number of dietary antigens which are important but the risk of contact with those antigens increases with greater dietary diversity. If you're playing Russian roulette the fewer live bullets in the chamber the greater are your chances of telling the tale.

These results need to be confirmed, but perhaps too much diversity in the diet of young babies is not a good thing, especially when there is a close family history of atopy.

ARCHIVIST

Archives of Disease in Childhood 1991; **66:** 598–602

Changes in body composition and energy expenditure after six weeks' growth hormone treatment

J W Gregory, S A Greene, R T Jung, C M Scrimgeour, M J Rennie

Abstract

Changes in body composition and energy expenditure were assessed in 15 children after six weeks of human growth hormone (hGH) treatment. Body composition measurements were made by stable isotope labelled water ($H_2{}^{18}O$) dilution, bioelectrical impedance, and skinfold thickness techniques. Energy expenditure was assessed both by indirect ventilated hood calorimetry (resting energy expenditure) and the stable isotope doubly labelled water ($^2H_2{}^{18}O$) technique (free living daily total energy expenditure). Mean increases in weight of 0·96 kg and fat free mass of 1·37 kg and a mean decrease in fat mass of 0·41 kg were observed. Significant increases both in resting energy expenditure and free living daily energy expenditure were detected. Absolute changes in fat mass and resting energy expenditure were correlated. The data suggest (i) that the increase in the fat free mass is the most significant early clinical measure of hGH response and (ii) that hGH increases the metabolic activity of the fat free mass. Monitoring such changes may be predictive of the efficacy of hGH in promoting growth.

Although growth hormone has been available for the treatment of children with short stature for approximately 30 years,[1] information on the association of the early metabolic effects of treatment to possible subsequent changes in body composition is limited. Metabolic studies (mostly made in the first one to two weeks of treatment) have shown that human growth hormone (hGH) is anabolic, indicated by nitrogen retention increasing within 24 hours[2–6] and reaching a maximum less than 14 days after initiation of treatment.[7] Also the triceps skinfold thickness, which is a measure of fat mass, decreases six to 10 weeks after the start of treatment. However, studies of other indices of body composition have been made only after longer periods of treatment (for example, total body potassium estimated by ^{40}K counting after seven months),[8] and little attempt has been made to compare the extent of the possible effects, early and late.

There is very little information, none recent, on the energy expenditure changes associated with treatment and the available information is inconsistent.[3 9] Most measurements of this sort were of resting energy expenditure and we are unaware of any attempts to measure free living daily total energy expenditure. Total energy expenditure may be affected by changes in well being which influence overall activity patterns. Furthermore, no attempts have been made to relate changes in total or resting energy expenditure to those in body composition in children treated with hGH. Accurate measurement of total energy expenditure in children was previously impossible in the free living state until the advent of the non-invasive doubly labelled water ($^2H_2{}^{18}O$) method using stable, non-radioactive isotopes.[10 11] We hypothesised that the early metabolic effects of hGH treatment would result in increased energy expenditure, which may be predictive of the subsequent anthropometric effect of treatment. We have therefore measured, before and after six weeks hGH treatment, changes in body composition using $H_2{}^{18}O$ dilution and compared the results with values obtained from two techniques more easily applicable routinely in the clinic, namely measurement of bioelectrical impedance and skinfold thickness. We have measured resting energy expenditure using indirect ventilated hood calorimetry and free living total energy expenditure using the $^2H_2{}^{18}O$ method to determine the effects of hGH treatment on energy expenditure and to see if such changes are related to changes in body composition. The results presented here are initial measurements from an ongoing study to assess the long term metabolic and energy expenditure effects of hGH and to discover whether early changes may be predictive of any long term growth promoting effects.

Patients and methods

Ethical approval for the study was obtained from the committee on medical ethics of Tayside Health Board. Fifteen patients (nine boys and six girls, table 1) participated, all of whom were recruited from the children's endocrine clinic and were to undergo a one year course of hGH treatment prescribed on clinical grounds. Nine patients had growth hormone insufficiency (concentration <10 μg/l (<20 mU/l) in response to a standard insulin stress test[12] and six had growth hormone concentrations ≥10 μg/l (≥20 mU/l) of whom four had normal variant short stature. The decision to treat case 3 (table 1) was based on a height velocity on the 10th centile for an 18 month period before entering the study. Before treatment with hGH, patients were admitted to the paediatric unit for a morning, having previously fasted from midnight. Height was measured using a Harpenden stadiometer and weight by a beam balance. Skinfold measurements (Holtain skinfold caliper) were made at the triceps, biceps, sub-

University of Dundee, Department of Child Health
J W Gregory
S A Greene

Department of Medicine
R T Jung

Department of Anatomy and Physiology
C M Scrimgeour
M J Rennie

Correspondence to:
Dr J W Gregory,
Department of Child Health,
The Medical School,
Framlington Place,
Newcastle upon Tyne
NE2 4HH.

Accepted 30 November 1990

Table 1 Pretreatment patient details

Case No	*Sex*	*Growth hormone concentration (μg/l)**	*Age (years)*	*Height SD score†*	*Height velocity (cm/year)‡*	*Weight (kg)*	*Diagnosis*
1	M	0·8	9·46	−1·03	3·73	27·40	Panhypopituitary
2	M	2·1	11·56	1·06	4·82	43·30	Craniopharyngioma
3	M	4·3	7·62	−3·12	8·24	15·65	IGHD
4	F	4·6	8·17	−2·09	3·43	19·00	Turner's syndrome
5	M	5·4	13·71	−0·92	8·27	38·30	After acute lymphoblastic leukaemia
6	M	5·9	7·84	−2·43	5·59	19·30	IGHD
7	F	6·8	11·85	−4·60	3·33	23·40	IGHD
8	F	7·0	7·65	−1·87	5·15	18·50	Turner's syndrome
9	F	8·9	10·29	−1·86	4·00	33·13	Turner's syndrome
10	F	11·8	11·01	−2·60	3·75	26·90	NVSS
11	M	11·9	12·61	−2·79	6·31	26·60	After acute lymphoblastic leukaemia
12	F	23·5	7·39	−2·15	4·68	18·15	Turner's syndrome
13	M	24·4	9·44	−3·20	3·08	22·10	NVSS
14	M	34·0	14·26	−3·81	4·63	32·60	NVSS
15	M	36·2	9·79	−3·17	3·96	20·70	NVSS
Mean		12·7	10·18	−2·31	4·86	25·66	
SE		3·0	0·59	0·35	0·42	2·09	

*Growth hormone response before hGH treatment; 1 μg/l=2 mU/l.
†Height expressed as SD score for chronological age.[35]
‡Height velocity calculated over a six month period before treatment.
IGHD, isolated growth hormone deficiency; NVSS, normal variant short stature.

scapular, and suprailiac sites.[13] Separate regression equations were used for converting the sum of the four skinfold thicknesses into body density for prepubertal[14] and adolescent[13] children. Percentage body fat was calculated[15] and thence fat mass and fat free mass could be derived for each child. Total body water was estimated from $H_2{}^{18}O$ dilution (measured in the basal and five hour post dose urine specimens) using the formula of Schoeller *et al*[16] and also by bioelectrical impedence which has been validated for use in children[17] and specifically in those with growth disorders.[18] Impedance measurements were made using a Holtain body composition analyser (Holtain Limited). The technique is simple to perform and highly acceptable to patients. Total body water (TBW) was calculated from the regression equation:

TBW=0·79+0·55 (Ht^2/Impedance)[18]

Assuming fat free mass (FFM) is composed of 73% water by weight,[19] then FFM=TBW/0·73 and

Fat mass=total body weight−FFM.

The doubly labelled water method for estimation of total energy expenditure has now been used in several centres with good precision (2–8%) in adults[11 20–21] and infants[22] and is now being applied to children.[23] It is based on the measurement of carbon dioxide production from the difference between the elimination rates of the deuterium ($^2H_2$) and ^{18}O with which the water is labelled. Because of the action of carbonic anhydrase, both water and bicarbonate pools are labelled with ^{18}O and the disappearance rate of ^{18}O is determined by the production of carbon dioxide and loss of water from the body. ^2H is lost only as water. The difference in the disappearance rates of ^{18}O and ^2H is proportional to the production of carbon dioxide and assuming a respiratory quotient (RQ) of 0·85,[24] total energy expenditure can be calculated using Weir's equation.[25]

At 0900 each patient took by mouth 0·3 g $H_2{}^{18}O$/kg estimated total body water (^{18}O was 10·4 atom %, Isotec Inc) and 0·12 g ^2H_2O/kg estimated total body water (^2H was 99·8 atom %, Sigma Chemical Company). Urine specimens for analysis were taken before and three, four, and five hours after ingestion of the isotope. For two weeks thereafter, the second morning urine specimen was collected (usually just before leaving for school). Isotope ratio measurements for ^{18}O and ^2H were carried out using a Finnigan MAT Delta D gas isotope ratio mass spectrometer fitted with an automated breath gas analysis system.[26] ^{18}O enrichment was measured after equilibration of 400 μl of urine with 5% carbon dioxide in 20 ml Vacutainers (Becton Dickinson) using the automated inlet system. ^2H was measured as $^2H_2$ after reduction of 8 μl urine samples with zinc at 450°C.[27] $^2H_2$ samples were manually introduced into the mass spectrometer.

After isotopic enrichment of the urine was measured, a rate constant for the disappearance of each isotope was determined. The integration method of Coward *et al* was employed to calculate the carbon dioxide production rate.[28]

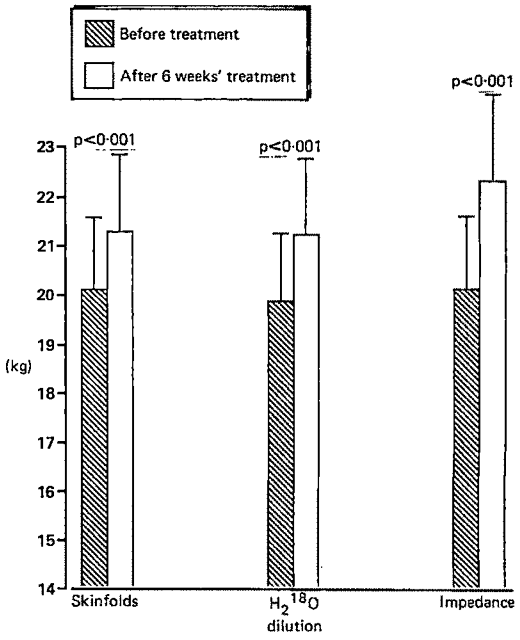


Figure 1 Mean (SE) changes in fat free mass by the three techniques.

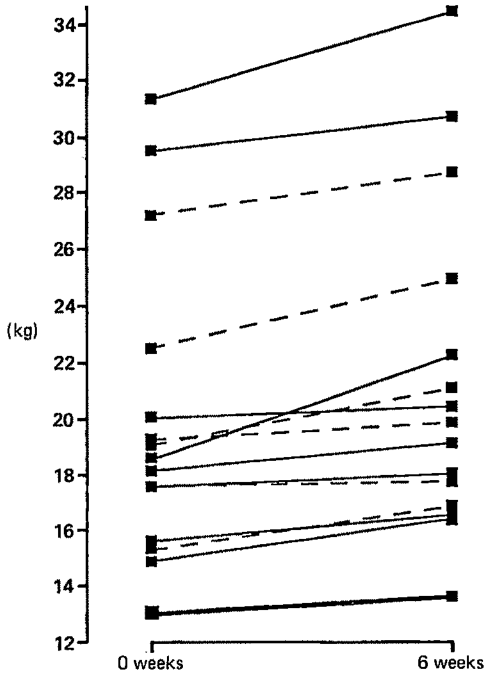


Figure 2 Individual changes in fat free mass by $H_2{}^{18}O$ dilution. Growth hormone concentration before treatment: ≥10 µg/l (≥20 mU/l), broken line; <10µg/l (<20 mU/l), solid line.

Total energy expenditure calculated by this method is thus a mean value for energy expenditure over a two week period.

Resting energy expenditure was estimated in a fasting state and thermoneutral environment by an indirect ventilated hood calorimeter[29] built by the medical physics department of Ninewells Hospital. Oxygen and carbon dioxide concentrations were measured by paramagnetic (Taylor, Servomex) and infrared (SS-200, Analytical Development Company Ltd) analyses respectively. Calorimeter operation and data processing were carried out using a Commodore 64 microcomputer; resting energy expenditure was calculated from Weir's equation.[25]

Table 2 Body composition before and after hGH treatment. Results are mean (SE)

	0 Weeks	*6 Weeks*	*p Value*
Weight (kg)	25·66 (2·09)	26·62 (2·23)	<0·005
Sum of 4 skinfolds (mm)	36·1 (3·6)	32·6 (3·5)	<0·05
Fat free mass (kg)*	19·83 (1·44)	21·20 (1·57)	<0·001
Fat mass (kg)*	5·83 (0·90)	5·42 (0·91)	NS

*By $H_2{}^{18}O$ dilution.

Patients were treated with subcutaneous injections of recombinant hGH (Norditropin, Novo Norkdisk) at a dose of 2 U daily. This resulted in a mean (SE) dose of 15·1 (0·8) U/m²/week or 0·57 (0·04) U/kg/week. Before and after treatment results were statistically analysed using a rank Wilcoxon test for paired data and the Spearman rank order correlation coefficient test. Significance was assigned at the level of 5%.

Results

BODY COMPOSITION (figs 1 and 2, table 2)

Pretreatment values of fat free mass in individual patients by each of the three techniques were highly correlated ($H_2{}^{18}O$ dilution compared with skinfolds, r=0·98, p<0·0005 and $H_2{}^{18}O$ dilution compared with impedance, r=0·95, p<0·0005) and all three methods gave similar values of the changes of fat free mass (fig 1). Therefore only body composition information obtained from $H_2{}^{18}O$ dilution is shown in

Table 3 Energy expenditure before and after hGH treatment. Results are mean (SE)

	0 Weeks	*6 Weeks*	*p Value*
Respiratory quotient	0·79 (0·02)	0·80 (0·01)	NS
Resting energy expenditure (kJ/day)	4088 (142)	4568 (158)	<0·005
Resting energy expenditure (kJ/kg fat free mass/day)	211 (10)	222 (11)	<0·05
Total energy expenditure (kJ/kg/day)	7171 (577)	7677 (609)	<0·05

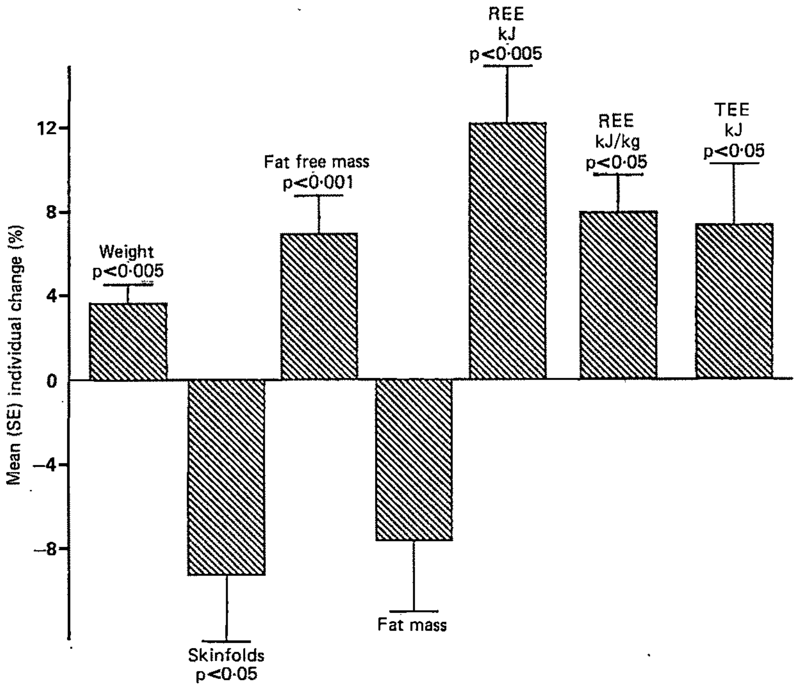


Figure 3 Effect of six weeks' treatment with hGH. REE, resting energy expenditure; TEE, total energy expenditure.

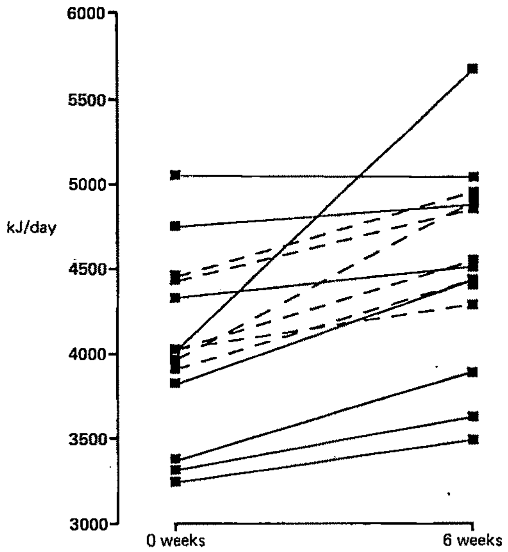


Figure 4 Individual changes in resting energy expenditure. Growth hormone concentration before treatment: ≥10 µg/l (≥20 mU/l), broken line; <10 µg/l (<20 mU/l), solid line.

fig 2 and table 2. Twelve of the 15 patients gained weight over the six week period. All 15 patients increased their fat free mass (fig 2).

ENERGY EXPENDITURE (figs 3 and 4, table 3) Because of the difficulty in persuading one 7 year old patient to lie still, reliable results of resting energy expenditure changes are available in only 14 of 15 patients. There was a significant mean increase of 12·1% ($p<0·005$) in resting energy expenditure in individual subjects over six weeks with only one patient (case 5) demonstrating a decrease over that time (fig 4). However, when resting energy expenditure was expressed/kg fat free mass, four patients (cases 2, 4, 5, and 11) showed a mean decrease of 2·8%, though the overall mean individual increase in resting energy expenditure/kg fat free mass of 7·9% was still significant ($p<0·05$). Measurement of total energy expenditure also showed a significant mean individual increase of 7·3% ($p<0·05$) over six weeks, although in three patients (cases 3, 5, and 13) the values did decrease. The mean changes in response to treatment are summarised in table 3 and fig 3.

Pretreatment resting and total energy expenditure correlated significantly with weight ($r=0·78$, $p<0·005$ and $r=0·68$, $p<0·05$ respectively) and with fat free mass ($r=0·87$, $p<0·005$ and $r=0·62$, $p<0·05$ respectively). Pretreatment resting and total energy expenditure were correlated ($r=0·54$, $p=0·05$). After six weeks of treatment with hGH there was an inverse correlation between absolute changes in fat mass and resting energy expenditure ($r=-0·53$, $p=0·05$). Absolute increases in resting and total energy expenditure over the six week period were positively correlated ($r=0·78$, $p<0·01$). However, none of these observed changes in energy expenditure was correlated with the differing doses of hGH (expressed either as U/kg/week or U/m^2/week) received by these patients.

Discussion

After six weeks of hGH treatment we observed significant increases in fat free mass that have not, so far as we know, been previously detected in children after such a short period of treatment. Unlike the results obtained by previous work in adults,[30] however, we have also observed a significant increase in weight, well above that anticipated over a six week period in a growing child. The study in adults has shown an early increase in fluid retention in response to hGH that might be the explanation for the observed significant increase in total body water and derived values of fat free mass measured in our study. A similar increase in fat free mass was detected by decreasing skinfold measurements, however, which might be considered an unlikely response to substantial production of oedema fluid. Therefore the increment in fat free mass indicated both by isotope dilution and impedance was probably genuine and not affected by oedema. Despite significant decreases in skinfold thicknesses, the mean decrease in fat mass was not significant and as net changes in weight were positive, it appears that the most sensitive measure of changes in body composition resulting from hGH treatment is that of an increase in fat free mass. This change in fat free mass can be easily monitored in the clinical situation by either skinfold thickness measurements taken by a single observer, or, if this is clinically inconvenient and different observers have to be involved, by the technique of bioelectrical impedence, which has a lower interobserver coefficient of variation.[18]

Unlike those of previous studies in children,[3 9] our results show a significant increase in both whole body resting energy expenditure and resting energy expenditure/kg fat free mass and also in whole body total energy expenditure. The percentage change is diminished when expressed as kJ/kg fat free mass reflecting the concurrent increase in absolute fat free mass. This increase in resting energy expenditure may be related to an increase in metabolic activity of lean tissue due to increased protein turnover. However, the increase in resting energy expenditure is significantly associated only with changes in fat mass and not fat free mass, perhaps suggesting that the stored fat is the energy source for subsequent metabolic activity of fat free mass. The increase in resting energy expenditure is not as great as that seen in a recently published study on adults,[30] probably reflecting the fact that some of our subjects were not as severely deficient in growth hormone and that measurements in the adult study were made after only four weeks of treatment. If the greatest metabolic effect of treatment (for example, nitrogen retention) occurs within two weeks of starting treatment and decreases thereafter, the measurable energy cost of such changes may be decreasing between four and six weeks.

If it is assumed that fat free mass contains 20·6% protein[31] and, as in children recovering from malnutrition and growing very rapidly, 1·4 g protein is synthesised/gram retained,[32] then the minimum energy cost of the protein deposited in the increased fat free mass can be calculated from 3·75 kJ/g protein deposited. This assumes four molecules ATP plus one molecule guanosine triphosphate are expended/mole peptide bond synthesised.[33] From these assumptions, the minimum energy cost of total protein synthesised for the mean increment of 1367 g in fat free mass (that is, net deposition of protein) measured over the initial six weeks of treatment (assuming an insignificant increase in fat free mass during the two week urine isotope collection before starting hGH) was 35 kJ/day. Thus only 7% of the observed mean increase in resting energy expenditure of 481 kJ/day can be accounted for by such mechanisms. As protein turnover (for which additional costs of protein breakdown, RNA turnover, and amino acid transport are small) and associated processes normally account for roughly 20% of resting energy expenditure,[33] much of the observed increase in resting energy expenditure must be related either to non-protein metabolic effects of hGH treatment or to a much greater than normal increase in protein synthesis/g protein deposited. This remains to be studied.

This study is, as far as we are aware, the first in which simultaneous measurements of resting energy expenditure and total energy expenditure have been made in children. It is of interest that the ratio of total energy expenditure to resting energy expenditure is 1·75:1, which is greater than the ratio of approximately 1·5:1 for adults.[34] This suggests that in children, a greater proportion of total energy expenditure is accounted for by activity than in adults. This and also the daily variability in behaviour likely to be exhibited by children is likely to be the explanation for the less significant increase in total energy expenditure than resting energy expenditure, though both increases were still correlated with each other and of a similar absolute magnitude. It appears that the increase in total energy expenditure is a reflection of the increase in the resting energy expenditure component of total energy expenditure and suggests that in children, hGH has no discernable effect on activity levels.

In conclusion, we have demonstrated that, in children undergoing hGH treatment, including those with normal variant short stature, clinically significant increases in fat free mass and body weight are detectable within six weeks of treatment. These changes are associated with increases in resting and total energy expenditure. Further studies are in progress to assess whether or not the extent of the observed changes are predictive of long term growth response to hGH treatment.

This work was supported by grants from the Biomedical Reseach Council of The Scottish Home and Health Department, Novo-Nordisk A/S, Birthright, The Wellcome Trust, The University of Dundee, and The European Social Fund. We are grateful to Dr S Ogston for statistical advice and to Mr M Rollo for assistance with some of the isotopic analysis.

1 Raben MS. Treatment of a pituitary dwarf with human growth hormone. *J Clin Endocrinol Metab* 1958;**18**:901–3.
2 Wright JC, Brasel JA, Aceto T, *et al*. Studies with human growth hormone (HGH). An attempt to correlate metabolic response during short-term administration with linear growth during prolonged therapy. *Am J Med* 1965;**38**: 499–516.
3 Prader A, Zachmann M, Poley JR, Illig R. The metabolic effect of a small uniform dose of human growth hormone in hypopituitary dwarfs and in control children. *Acta Endocrinol (Copenh)* 1968;**57**:115–28.
4 Clayton BE, Tanner JM, Vince FP. Diagnostic and prognostic value of short-term metabolic response to human growth hormone in short stature. *Arch Dis Child* 1971;**46**:405–13.
5 Rudman D, Kutner MH, Fleming GA, *et al*. Effect of 10-day courses of human growth hormone on height of short children. *J Clin Endocrinol Metab* 1978;**46**:28–35.
6 Dahms WT, Owens RP, Kalhan SC, Kerr DS, Danish RK. Urea synthesis, nitrogen balance, and glucose turnover in growth-hormone-deficient children before and after growth hormone administration. *Metabolism* 1989;**38**:197–203.
7 Henneman DH, Henneman PH. Effects of human growth hormone on levels of blood and urinary carbohydrate and fat metabolites in man. *J Clin Invest* 1960;**39**:1239–45.
8 Collipp PJ, Curti V, Thomas J, Sharma RK, Maddaiah VT, Cohn SH. Body composition changes in children receiving human growth hormone. *Metabolism* 1973;**22**:589–95.
9 Brasel JA. Oxygen consumpton and growth. In: Cheek DB, ed. *Human growth. Body composition, cell growth, energy and intelligence*. Philadelphia: Lea and Febiger, 1968:474–93.
10 Lifson N, Gordon GB, McClintock R. Measurement of total carbon dioxide production by means of D_2O^{18}. *J Appl Physiol* 1955;**7**:704–10.
11 Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol* 1982;**53**:955–9.
12 Hughes IA. *Handbook of endocrine tests in children*. Bristol: Wright, 1986:133–4.
13 Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. *Br J Nutr* 1967;**21**:681–9.
14 Brook CGD. Determination of body composition of children from skinfold measurements. *Arch Dis Child* 1971;**46**: 182–4.
15 Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henschel A, eds. *Techniques for measuring body composition*. Washington DC: National Academy of Science, 1961:223–44.
16 Schoeller DA, van Santen E, Peterson DW, *et al*. Total body water measurement in humans with ^{18}O and ^{2}H labeled water. *Am J Clin Nutr* 1980;**33**:2686–93.
17 Davies PSW, Preece MA, Hicks CJ, Halliday D. The prediction of total body water using bioelectrical impedance in children and adolescents. *Ann Hum Biol* 1988;**15**:237–40.
18 Gregory JW, Greene SA, Scrimgeour CM, Rennie MJ. Body water measurement in growth disorders: a comparison of bioelectrical impedance and skinfold thickness techniques with isotope dilution. *Arch Dis Child* 1991;**66**:220–2.
19 Pace N, Rathbun EN. Studies on body composition. The body water and chemically combined nitrogen content in relation to fat content. *J Biol Chem* 1945;**158**:685–91.
20 Klein PD, James WPT, Wong WW, *et al*. Calorimetric validation of the doubly-labelled water method for determination of energy expenditure in man. *Hum Nutr:Clin Nutr* 1984;**38C**:95–106.
21 Prentice AM, Coward WA, Davies HL, *et al*. Unexpectedly low levels of energy expenditure in healthy women. *Lancet* 1985;**i**:1419–22.
22 Roberts SB, Coward WA, Schlingenseipen K-H, Nohria V, Lucas A. Comparison of the doubly labeled water ($^{2}H_2{}^{18}O$) method with indirect calorimetry and a nutrient-balance study for simultaneous determination of energy expenditure, water intake, and metabolizable energy intake in preterm infants. *Am J Clin Nutr* 1986;**44**:315–22.
23 Schoeller DA, Levitsky LL, Bandini LG, Dietz WW, Walczak A. Energy expenditure and body composition in Prader-Willi syndrome. *Metabolism* 1988;**37**:115–20.
24 Black AE, Prentice AM, Coward WA. Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. *Hum Nutr: Clin Nutr* 1986;**40C**:381–91.
25 Weir JBdeV. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949;**109**:1–9.
26 Scrimgeour CM, Rennie MJ. Automated measurement of the concentration and ^{13}C enrichment of carbon dioxide in breath and blood samples using the Finnigan MAT breath gas analysis system. *Biomed Environ Mass Spectrom* 1988; **15**:365–7.
27 Wong WW, Lee LS, Klein PD. Deuterium and oxygen-18 measurements on microliter samples of urine, plasma, saliva, and human milk. *Am J Clin Nutr* 1987;**45**:905–13.
28 Coward WA, Prentice AM, Murgatroyd PR, *et al*. Measurement of CO_2 and water production rates in man using ^{2}H, ^{18}O-labelled H_2O; comparisons between calorimeter and isotope values. In: van Es AJH, ed. *Human energy metabolism: physical activity and energy expenditure measurements in epidemiological research based upon direct and indirect calorimetry*. Euro-Nut, The Hague: Cip-Gegevans Koninklijke Bibliotheck, 1985:126–8. (Series number 5.)
29 Crisp JA, Murgatroyd PR. A versatile and mobile microcomputerised system for indirect calorimetry. In: *Human energy metabolism: physical activity and energy expenditure measurements in epidemiological research based upon direct and indirect calorimetry*. Euro-Nut, The Hague: Cip-Gegevans Koninklijke Bibliotheck, 1985:44–45. (Series number 5.)
30 Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* 1989;**321**:1797–803.
31 Forbes GB. *Human body composition. Growth, aging, nutrition, and activity*. New York: Springer-Verlag, 1987:229.
32 Reeds PJ, Harris CI. Protein turnover in animals: man in his context. In: Waterlow JC, Stephen JML, eds. *Nitrogen metabolism in man*. London: Applied Science Publishers, 1981:391–408.
33 Waterlow JC, Millward DJ. Energy cost of turnover of protein and other cellular constituents. In: Wieser W, Gnaiger E, eds. *Energy transformations in cells and organisms*. Stuttgart: Georg Thieme Verlag, 1989:277–82.
34 Sims EAH, Danforth E. Expenditure and storage of energy in man. *J Clin Invest* 1987;**79**:1019–25.
35 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966;**41**:613–35.

Archives of Disease in Childhood 1991; **66:** 603–607

Infantile meningitis in England and Wales: a two year study

J de Louvois, J Blackbourn, R Hurley, D Harvey

Karim Centre for Meningitis Research, Royal Postgraduate Medical School Institute of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, London W6 0XG
J de Louvois
J Blackbourn
R Hurley
D Harvey

Correspondence to:
Dr Harvey.

Accepted 10 December 1990

Abstract

A two year prospective study identified 1922 cases of meningitis in children under 1 year of age. A further 201 cases were identified from other sources. The annual incidence of meningitis during the first year of life was 1·6/1000; during the first 28 days of life it was 0·32/1000, and among postneonatal infants it was 1·22/1000. The male:female ratio was 1·4:1. The overall case fatality rate was 19·8% for neonates and 5·4% for postneonatal infants. Two thirds of deaths identified in the study, 50% of all deaths, were not attributed to meningitis by the Office of Population Censuses and Surveys. Group B β haemolytic streptococci (28%), *Escherichia coli* (18%), and *Listeria monocytogenes* (5%) were most frequently isolated from neonates and *Neisseria meningitidis* (31%), *Haemophilus influenzae* (30%), and *Streptococcus pneumoniae* (10%) from postneonatal infants. At 2–6 months of age *N meningitidis* meningitis was most common, and at 7–12 months *H influenzae* predominated. Meningitis caused by group B β haemolytic streptococci occurred up to 6 months of age and had a consistent mortality of 25%. Neonatal meningitis due to Gram negative enteric rods had a mortality of 32%. Low birth weight was a significant predisposing factor for both neonates and postneonatal infants. In both groups mortality was significantly higher among children admitted in coma. There was no seasonal variation in incidence in either group. Neonates were treated with either chloramphenicol (50%) or gentamicin (48%) usually in combination with a penicillin; 40% received a third generation cephalosporin. Of the 1472 postneonatal infants treated 84% received chloramphenicol with a penicillin and 10% received a third generation cephalosporin. Relapse occurred in 49 patients and three died. Eighteen babies coned as a result of raised intracranial pressure, including four neonates, and four died. Mortality among the 133 (7%) children who received steroids was significantly higher than in the rest of the study group.

Meningitis in infancy is a life threatening infection with a high mortality. Neurological sequelae are common, especially in the newborn where long term effects are found in more than a quarter of survivors.[1 2] Despite its serious nature there is little information on the incidence of meningitis in England and Wales. Although a number of centres, including the Communicable Diseases Surveillance Centre of the Public Health Laboratory Service and the Meningococcal Reference Laboratory, collect data provided to them on a voluntary basis there is known to be considerable under reporting. There is a high level of under reporting also in local studies, even for meningococcal meningitis.[3–6] The only comprehensive information on the recent incidence of meningitis in Great Britain comes from a few independent studies with small numbers of patients. A study of cases from the North West Thames health region for the period 1969–73 identified 76 cases in newborn babies and 231 cases in postneonatal infants (28–365 days of age); the case fatality rates were 43% and 13% respectively.[7] The incidence of meningitis in the newborn was 0·26/1000 live births. Meningitis was diagnosed only at necropsy in 28% of fatal cases; many of them were not indexed by Hospital Activity Analysis (HAA).

The present study was undertaken to determine prospectively the incidence of meningitis among children under 1 year of age in England and Wales.

Subjects and methods

STUDY ORGANISATION

With the collaboration of 566 consultant paediatricians we undertook to identify all cases of acute meningitis in children under 1 year of age in England and Wales from September 1985 to August 1987. At the beginning of each month each paediatrician received a prepaid card which inquired whether they had managed any cases of acute infantile meningitis during the previous month. After each notification, clinical and laboratory information was collected on standard forms sent to the paediatrician and consultant microbiologist involved in the management of each case. Written permission was obtained from the paediatricians so that information on cases notified in confidence to the Communicable Diseases Surveillance Centre, Colindale (CDSC) and the Meningococcal Reference Laboratory, Manchester, could also be used. Death certificates on all babies recorded as having died of meningitis were obtained from the Office of Population Censuses and Surveys (OPCS).

ADMISSION CRITERIA

The initial criterion for inclusion in the study was an 'intention to treat' by the paediatrician of babies with clinical signs and symptoms suggestive of meningitis. Babies who had viable bacteria, viruses, or detectable bacterial antigen in the cerebrospinal fluid or whose white cell counts in the cerebrospinal fluid were sufficiently abnormal ($>20\times10^6$/l) to warrant a diagnosis of meningitis were finally accepted into the study. Babies whose clinical condition was highly suggestive of meningitis but who were deemed too ill to warrant a lumbar puncture were also included. Babies with spina bifida and ventricular shunt infections were excluded.

Bacterial isolates and residual samples of cerebrospinal fluid were sent to our centre when available. No attempt was made to influence the management or treatment of babies admitted to the study nor to alter the protocol for local laboratory investigations carried out on samples.

Results

The monthly inquiry cards identified 1922 cases of meningitis in England and Wales during the two year period. Information on 201 additional cases (23 neonates; 133 postneonatal infants between 1 month and 1 year of age, and 45 infants of unspecified age under 1 year) was obtained from the CDSC (n=138), the Meningococcal Reference Laboratory (n=27) and the OPCS (n=36). These 201 cases are included in the calculation of incidence and mortality but are excluded from other analysis. Information from all sources identified a total of 2123 cases of meningitis during the first year of life. The mean birth rate for England and Wales during the study period was 658 700 per annum; giving an annual incidence of meningitis during the first year of life of 1·61/1000. There were 423 cases during the first 28 days of life (an incidence of 0·32/1000) and 1605 cases in the period 29–365 days (an incidence of 1·22/1000 population). There were another 95 cases (50 from the survey and 45 from other sources) among babies less than 1 year of age whose exact age was not known. The male:female ratio was 1·4:1 for both neonates and postneonatal infants. Culture results for the cases identified from all sources are shown in table 1.

Table 1 Meningitis in the first year of life in England and Wales 1985–7: causative organisms. Results are number (%)

	Neonates (n=423)	*Postneonatal infants (n=1605)*
Group B β haemolytic streptococci	118 (28)	50 (3)
Escherichia coli	78 (18)	29 (2)
Listeria monocytogenes	23 (5)	1 (<1)
Haemophilus influenzae	9 (2)	477 (30)
Neisseria meningitidis	11 (3)	490 (31)
Streptococcus pneumoniae	19 (5)	158 (10)
Other Gram positive bacteria	15 (4)	26 (2)
Other Gram negative bacteria	28 (7)	31 (2)
Viruses	16 (4)	37 (2)
Mycoplasma hominis	3 (<1)	1 (<1)
Candida albicans	4 (1)	5 (<1)
Other microorganisms	5 (1)	9 (<1)
Cerebrospinal fluid sterile or not collected	92 (22)	270 (17)
Unknown	2 (<1)	21 (1)

Of the 1922 cases of meningitis identified in our study, 400 were in babies less than 29 days of age and 1472 were aged 29–365 days. After the initial notification no further information was obtained on the remaining 50 babies and these are omitted from further analysis. The overall case fatality rate was 79/400 (19·8%) for neonates and 5·4% (79/1472) for postneonatal infants. A total of 104 of 158 deaths (66%) identified by us were not coded as attributable to meningitis by OPCS. They account for 51% (104/201) of all deaths from meningitis in children under 1 year of age. In addition, 12% of the death certificates coded by OPCS as cases of meningitis contained no mention of the condition. Among the deaths notified to OPCS were 23 which were not notified to the study. Some of these are known to be infants who did not come to the attention of the paediatricians. Among babies whose cerebrospinal fluid cultures were positive, the overall mortality rate was 10% (29% for neonates and 6% for postneonatal infants) in bacterial meningitis and nil in viral meningitis. There was a significantly higher mortality among babies with viable bacteria in the cerebrospinal fluid compared with those with only a pleocytosis; for neonates ($p<0·0001$, odds ratio 10·44, confidence intervals 3·1 to 34·8); and for postneonatal infants ($p<0·001$, odds ratio 3·59, confidence intervals 1·4 to 9·1). White cell counts in the cerebrospinal fluid were $>100\times10^6$/l in 79% of neonates and 85% of postneonatal infants. Only 8·5% of neonates and 6% of infants with culture positive meningitis had cerebrospinal fluid cell counts $<10\times10^6$/l.

Clinical details on the 1872 patients at the time of diagnosis are shown in table 2. Prematurity and low birth weight were predisposing factors in both the neonatal and the postneonatal infants groups. A birth weight of <2000 g was significantly more common in both patient groups ($p<0·001$) than the 2·4% of the population in England and Wales with a birth weight of <2000 g.[8] Meningitis was 10 times more common among neonates weighing <2000 g than those of >2000 g birth weight.

Table 2 Clinical details at the time of diagnosis on 1872 babies with meningitis. Results are number (%)

	Total (n=1872)	*Neonates (n=400)*	*Postneonatal infants (n=1472)*
Less than 30 weeks' gestation	75	37 (9)	38 (3)
Less than 2000 g at birth	163	78 (20)	85 (6)
On admission:			
In coma	205	42 (11)	163 (11)
Convulsions	325	82 (21)	243 (17)
Rash	248	18 (5)	230 (16)
Antibiotic treatment in previous 48 hours	420	82 (21)	338 (23)
Congenital anomaly	107	29 (7)	78 (5)
Hydrocephalus	46	12 (3)	34 (2)
Previous surgery	68	13 (3)	55 (4)
History of otitis media	120	0	120 (8)
Antecedent history	275	39 (10)	236 (16)

Among postneonatal infants the ratio was 2·5:1. Twelve per cent of neonates and postneonatal infants were admitted in coma; in both groups, this was associated with a significantly increased mortality ($p<0{\cdot}0001$). A rash was present at diagnosis in 16% of infants, but only 5% of neonates. All of the babies with a history of otitis media were in the infant group. Recent upper respiratory tract infection or other antecedent history of infection was also more common among infants (16%) than neonates (10%). Altogether 94% of infants and 45% of neonates with meningitis were admitted from home and 23% had received antibiotics from the general practitioner before admission. There was no seasonal variation in incidence of meningitis in either group of patients.

Seventy one babies did not have a sample of cerebrospinal fluid taken before treatment, because either they were considered to be too sick or the procedure failed; 23/71 (32%) of these babies died compared with 7% of babies who had cerebrospinal fluid collected. Mid-treatment samples of cerebrospinal fluid were collected from 41% of patients and samples after treatment from 20%.

Most patients received more than one antibiotic, only 172 (1%) received monotherapy. The number of babies who received each antibiotic and the percentage of neonates and infants treated with each antimicrobial agent are shown in table 3. In half the neonates the regimen was based on chloramphenicol and in half on gentamicin. In addition most patients received penicillin, ampicillin, or a third generation cephalosporin.

Among infants chloramphenicol was the most widely used antibiotic (84%) usually in combination with penicillin or ampicillin. Third generation cephalosporins were used for the treatment of 46% neonates but only 14% of postneonatal infants. No babies received cephalosporin only. Sulphonamides were included in the treatment regimens of 11% neonates and 17% of postneonatal infants.

Fifty eight per cent of patients were treated for seven to 14 days and 12% for 21 days. Altogether 29% of neonates compared with 14% of postneonatal infants were treated for more than 14 days. Antibiotic treatment was changed after sensitivity testing in 15% of neonates and 6% of postneonatal infants. Seven hundred and thirteen patients received barbiturates (50% of neonates and 40% of postneonatal infants) and 133 received steroids (7% of neonates and 8% of postneonatal infants); included in these figures are 96 patients who received both. Ten per cent of neonates and 26% of postneonatal infants who died had received steroids. Convulsions at the time of diagnosis were reported in 325 babies, 17% of the study population. Postmortem examinations were carried out on 70/159 babies who died (44%).

Table 3 Antibiotic treatment of 1872 babies with meningitis. Results are number (%)

	Total (n=1683/ 1872)*	*Neonates (n=360*/ 400)*	*Postneonatal infants (n=1323*/ 1472)*
Chloramphenicol	1293	180 (50)	1113 (84)
Gentamicin	284	174 (48)	110 (8)
Other aminoglycosides	45	30 (8)	15 (1)
Penicillin	1220	225 (62)	995 (75)
Ampicillin	377	79 (22)	298 (23)
Other penicillins	46	27 (7)	19 (1)
Cefotaxime	202	94 (26)	108 (8)
Ceftazidime	84	54 (15)	30 (2)
Other cephalosporins	71	20 (5)	51 (4)
Sulphonamides	259	40 (11)	219 (17)
Other antibiotics	18	9 (2)	9 (1)

*Patients with treatment data.

Ventriculitis, hydrocephalus, or convulsions were reported as complications in 346 (21%) of patients and were more common in the newborn (33%) than in postneonatal infants (18%). Forty nine patients relapsed after treatment: 15 (5%) neonates and 34 (3%) postneonatal infants; three of these died. Among patients who relapsed 21% were in coma on admission compared with approximately 11% for the total group; 25% had already received treatment for more than 21 days compared with 6% for the total population. Only 9% of patients who relapsed received antibiotics before admission compared with more than 20% of the total population. The white cell count in the cerebrospinal fluid among patients who relapsed was not different from that of the total population. Thirty one (86%) had cell counts $>100\times10^6$/l cerebrospinal fluid at the time of the first diagnostic tap compared with 81% of the total population.

Paediatricians reported that 18 babies coned after lumbar puncture (four neonates and 14 postneonatal infants) as a result of raised intracranial pressure; four of them died. All the babies who coned weighed more than 2000 g at birth but three were less than 36 weeks' gestation. Twelve (66%) were feverish (>38°C) at the time of diagnosis and only one had received antibiotics during the previous 48 hours, four were admitted in coma, four had convulsions, and one had a rash. None of the patients who coned had a congenital anomaly, one had developed hydrocephalus before admission, and one had a history of otitis. Results from the cerebrospinal fluid were available from 15 of the patients who coned; in 14 (93%) the white cell count was $>100\times10^6$/l. The course of the illness for 12/16 (75%) patients who coned was complicated by convulsions, ventriculitis, or hydrocephalus compared with 21% of the total population. Information on the other two patients was not available. Two patients relapsed after treatment was completed.

The organisms isolated from the cerebrospinal fluid are shown in table 1. Among neonates, group B β haemolytic streptococci were most frequently isolated followed by *E coli* and *L monocytogenes*. A wide range of other bacteria were implicated in neonatal meningitis whereas among postneonatal infants *N meningitidis, H influenzae* and *S pneumoniae* accounted for 70% of all cases and 89% of bacteriologically proved meningitis. The case fatality rate was highest in neonates with meningitis due to enteric Gram negative rods: 32% compared with 22% for group B β haemolytic streptococcal meningitis, 5% among cases due to *L monocytogenes*, and 2% among culture negative cases.

E coli and group B β haemolytic streptococci were also significant causes of meningitis

Table 4 Meningitis in the first year of life in England and Wales 1985–7: death by organism. Results are number (%)

	Neonates (n=400)	*Postneonatal infants (n=1472)*
Group B β haemolytic streptococci	27/112 (24)	11/44 (25)
Escherichia coli	18/72 (25)	5/27 (19)
Listeria monocytogenes	2/19 (11)	0/1
Haemophilus influenzae	2/9 (22)	17/445 (4)
Neisseria meningitidis	0/10	19/433 (4)
Streptococcus pneumoniae	3/18 (17)	12/150 (8)
Other Gram negative organisms	13/26 (50)	5/27 (19)
Other Gram positive organisms	5/14 (36)	3/23 (13)
Viruses	0/16	0/37
Mycoplasma hominis	2/3 (66)	0/1
Candida albicans	3/4 (75)	1/5 (20)
Other microorganisms	1/5 (20)	1/9 (11)
Sterile cerebrospinal fluid	3/92 (3)	5/270 (2)
Total No deaths	79	79

outside the neonatal period and together accounted for 8% cases during the second to sixth months of life. Throughout the first year of life meningitis due to *E coli* and group B β haemolytic streptococci was associated with a high mortality rate. Cases and deaths by organism for patients in the two groups are shown in table 4. Meningitis was most common during weeks one and three of life. *N meningitidis* (29%) was the commonest cause of meningitis in children 2–6 months of age, and among children aged 7–12 months *H influenzae* (46%) was most frequently isolated. The mortality rate among postneonatal infants infected with *S pneumoniae* was twice as high (6%) as that after infection with meningococci or haemophilus.

Discussion

This study confirms recent reports that meningitis in England and Wales is still significantly under reported.[3–6] Detailed observations on reporting will be the subject of a separate communication. Information on a large number of cases notified to us was not sent to CDSC or the Meningococcal Reference Laboratory. Consultant paediatricians notified us of 158 babies who had died of meningitis; 104 (66%) of these were not coded by OPCS as cases of meningitis. In addition there were 43 children who died of meningitis, 22% of all deaths, who were not notified to the study. Subsequent inquiry revealed that many of these cases had not come to the attention of the paediatricians. This figure (22%) compares with the 29% reported by Goldacre for infants in whom meningitis was diagnosed only at necropsy.[7] Accurate calculation of the mortality associated with meningitis during the newborn period is now impossible as OPCS no longer report the causes of death occurring during the first 28 days of life. It is disturbing that 12% of death certificates for babies coded by OPCS as having died from meningitis contained no mention of this condition.

The incidence of neonatal meningitis in our study (0·32/1000 live births) is higher than that reported by Goldacre (0·26/1000 live births) for the period 1969–73, using essentially the same diagnostic critiera.[7] This would support the suggestion that the incidence of meningitis among the newborn is increasing; however, comparison of the figures for the North West Thames hospital region for 1968–73 and 1985–7 shows no increase. There were 16 cases of neonatal meningitis per year for the period 1968–73 compared with 10 per year during 1985–7. Among postneonatal infants there were 46 and 40 cases per year respectively. Although there may have been no increase in the incidence of meningitis, the case fatality rate for neonatal meningitis has fallen from 43% reported by Goldacre to 20% in the present study. Among postneonatal infants the mortality rate has fallen from 13% for the period 1969–73 to 5% for the period 1985–7.

Meningitis occurred significantly more frequently ($p<0·001$) among neonates who were born prematurely or were of low birth weight confirming previous reports.[9] There was a significant association also ($p<0·001$) between low birth weight (<2000 g) and meningitis among postneonatal infants compared with the national incidence of birth weight below 2000 g.[8] Meningitis due to Gram negative organisms has a higher mortality than that due to Gram positive bacteria, as has been reported previously.[10, 11] Mortality is significantly lower for postneonatal infants in general but it remains high throughout the first year of life for babies infected with *E coli* and group B β haemolytic streptococci. Irrespective of the clinical presentation or the number of white cells present in the cerebrospinal fluid, mortality was significantly lower for both neonates and postneonatal infants whose cerebrospinal fluid culture results were negative. Some of these may have been cases of undiagnosed viral meningitis, and in others the prompt use of antibiotics by the general practitioner may have effectively sterilised the cerebrospinal fluid before a lumbar puncture was performed.

In the majority of laboratories in England and Wales viral studies are not part of the routine investigation of suspected infantile meningitis. Chonmaitree *et al* studied 111 patients who had viral investigations because of suspected meningitis; 63 of these patients were under 1 year of age.[12] Enteroviruses were isolated from 46 (41%) of the population and from 60% of those under 1 year of age. The isolation of a virus shortened hospital stay and reduced the unneccessary use of antibiotics. Clearly, viral culture of cerebrospinal fluid and other appropriate specimens, together with serology, should be part of the routine investigation of meningitis in the very young.

Only 133 (7%) of the study population received steroids during the acute phase of their illness. Mortality among those receiving steroids was significantly higher ($p<0·001$) than for the remainder of the population. This is not in agreement with other studies and probably reflects the use of steroids in the most severely ill patients. In controlled studies on the use of dexamethasone in the treatment of meningitis, Lebel *et al* reported that administration before the first dose of antibiotics does not effect the mortality rate but reduces the duration of fever and significantly lowers the incidence of sensorineural hearing loss associated with acute bacterial meningitis.[13] The beneficial effects of dexamethasone have been reported by other workers also.[14 15] No information is available on the duration of fever in the group treated with steroids in our study. We are currently following up the study population, and matched controls, until the fifth birthday in order to determine the incidence of deafness and other long term sequelae from infantile meningitis.

We thank all the paediatricians and microbiologists concerned in this study for allowing us to study their patients and for so willingly providing the information requested. Without their cooperation this study would not have been possible. The study was supported financially by donations received by the Karim Centre for Meningitis Research.

1 Shohet I, Davidsson S, Shahar E, Lison M, Barzilay Z, Rubenstein E. Bacterial meningitis, a follow-up of 115 children. *Isr J Med Sci* 1982;**18**:779–84.

2 Mulhall A, de Louvois J, Hurley R. Efficacy of chloramphenicol in the treatment of neonatal and infantile meningitis. *Lancet* 1983;**i**:284–7.

3 Harvey IM, Palmer SR, Peters TJ. Meningitis: can we trust the statistics? *Health Trends* 1989;**21**:73–6.

4 Lambert PM. Recent trends in meningococcal infection. *Community Med* 1973;**129**:279–81.

5 Davies LA. Assessing the value of different sources of information on meningococcal disease. *Community Med* 1989;**11**:239–46.

6 Cartwright KAV, Stuart JM, Noah ND. An outbreak of meningococcal disease in Gloucestershire. *Lancet* 1986;**ii**: 558–61.

7 Goldacre MJ. Acute bacterial meningitis in childhood. *Lancet* 1976;**i**:28–31.

8 Government Statistical Service. *OPCS Monitor. Infant and perinatal mortality 1986: birthweight.* London: HMSO, 1988. (DH3 88/1).

9 Klein JO, Marcy SM. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant.* 3rd Ed. Philadelphia: WB Saunders, 1990:601–56.

10 Mulder CJJ, Zanen HC. A study of 280 cases of neonatal meningitis in the Netherlands. *J Infect* 1984;**9**:177–84.

11 Pearse RG, Roberton NRC. Infection in the newborn. *Textbook of neonatology.* Edinburgh: Churchill Livingstone, 1986:725–81.

12 Chonmaitree T, Menegus MA, Powell KR. The clinical relevance of CSF viral culture. *JAMA* 1982;**247**:1843–7.

13 Lebel MH, Freij BJ, Syrogiannopoulos GA, *et al.* Dexamethazone therapy for bacterial meningitis: results of two double blind placebo controlled studies. *N Engl J Med* 1988;**319**:964–71.

14 Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethazone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J* 1989; **8**:848–51.

15 Anonymous. Steroids and meningitis. *Lancet* 1989;**i**:1307–8.

Autism, gene pools, and the Mormons

Autism affects between two and five of every 10 000 and is three or four times more common in males than females.[1] The cause is unknown but genetic factors seem more important than acquired disease. The concordance rates are 64% in dizygotic and 9% in monozygotic twins. An epidemiological survey of the state of Utah has provided useful information. A total of 241 people with autism were ascertained and the medical records of 233 of them and of 62 of their non-autistic siblings were examined (Mason-Brothers *et al, Pediatrics* 1990;**86**:514–9). There were no significant differences between autistic and non-autistic subjects as regards prenatal, perinatal, or postnatal factors.

Previously published results from the same survey gave usable information for genetic counselling.[2] The recurrence risk overall was 8·6% but it varied according to the sex of the first autistic child; if the first child was male the recurrence risk was 7%, if female 14·5%. The authors are careful to point out that the strength of the Mormon church in Utah does not appear to have had any significant effect on the gene pool.

ARCHIVIST

1 Smalley SL, Asarnow RF, Spence MA. Autism and genetics. A decade of research. *Arch Gen Psychiatry* 1988;**45**:953–61.

2 Ritvo ER, Jorde LB, Mason-Brothers A, *et al.* The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counselling. *Am J Psychiatry* 1989;**146**:1032–6.

Archives of Disease in Childhood 1991; **66**: 608–611

Increasing incidence of coeliac disease in Sweden

H Ascher, I Krantz, B Kristiansson

Department of Pediatrics I, Gothenburg University, East Hospital, S 416 85 Göteborg, Sweden
H Ascher
B Kristiansson

Nordic School of Public Health, Göteborg, Sweden
I Krantz

Correspondence to:
Dr Ascher.

Accepted 15 November 1990

Abstract

Changes in the incidence of coelic disease was studied among children born in Göteborg, Sweden, between 1970 and 1988. A total of 188 patients with coeliac disease were found. Of these, 83% were less than 2 years old at the time of their first duodenal biopsy and 74% of them have so far been verified according to the criteria of the European Society for Gastroenterology and Nutrition (ESPGAN). The cumulative incidence at 2 years of age/1000 liveborn infants increased significantly from 0·31 in the first birth cohort to 2·93 in the last. This increase could only partly be explained by improvements in detection. Weight for age at diagnosis was generally considerably below the reference value, but was slightly less affected towards the end of the period. The increase in incidence of coeliac disease is the first reported since the middle 1970s and makes the disease one of the most common chronic diseases among Swedish children.

Since the middle of the 1970s, coeliac disease in childhood has been reported to be decreasing in England,[1-4] Scotland,[5] and Ireland.[6] The incidence and clinical picture have remained unchanged in Italy.[7] In Finland a decrease in the number of cases diagnosed, together with a changing clinical pattern of a late start and mild course, led to the conclusion that the real incidence was probably unchanged.[8]

In this study we report the changes in the incidence of childhood coeliac disease during the last 20 years in Göteborg, the second largest city in Sweden, which had 435 842 inhabitants in 1979 (the middle of the study period) and a computer based population register. The city, like Sweden in general, has a comprehensive child health service with child health centres attended by 98% of all infants and young children.[9]

Patients and methods

All children with coeliac disease who were attending the Department of Paediatrics, University of Gothenburg, at East Hospital, Göteborg, Sweden were investigated retrospectively. The hospital has the only paediatric department in the city and is the only place where small intestinal biopsy is done. All children with coeliac disease born between 1970 and 1988 were identified. Those born outside the city were excluded. The starting year 1970 was chosen because small intestinal biopsy was not a routine investigation before that.

To confirm the diagnosis of coeliac disease, at least three small intestinal biopsy specimens were taken when the child was eating different diets according to the criteria of the European Society for Gastroenterology and Nutrition (ESPGAN).[10, 11] Four children, born in 1971, 1972, 1973, and 1980 (the first of them being more than 2 years old at the time of the first small intestinal biopsy) were regarded as verified according to the ESPGAN criteria, although they had not had a small intestinal biopsy specimen taken while on a gluten free diet. Children with typical symptoms, an initial flat mucosa, and a distinct clinical response to a gluten free diet but who had not yet fulfilled all the criteria, were also included in the study. Children with suspected coeliac disease but with a less convincing clinical course or histopathological changes were excluded.

The small intestine was biopsied under fluoroscopic control with a Watson capsule, paediatric size. The histopathological picture was classified according to a five point scale by a pathologist who specialised in gastroenterological pathology.[12]

The age at diagnosis, defined as the time of the first small intestinal biopsy, was determined. Cases diagnosed before the age of 2 years were identified. The number in each birth cohort was divided by the number of liveborn infants in Göteborg of that year, giving the cumulative incidence at the age of 2 years for each birth cohort. For each patient who was less than 2 years old at the time of diagnosis, the weight for age at the first biopsy expressed as SD scores of the reference population was calculated.[13] Weight for age, onset of symptoms, and time from onset to diagnosis, were consecutively recorded and extracted.

To analyse the significance of differences between proportions we used the χ^2 test. Linear regression was used to assess time trends.

Results

Altogether 188 children with coeliac disease born between 1970 and 1988 were investigated and treated at the department of paediatrics up to 1 June 1990. Of the total, 134 (71%) have been verified according to the ESPGAN criteria.[10, 11]

Between 1971 and 1975, a mean of five new cases of coeliac disease were diagnosed each year. This number increased to 18 for the years 1985–9 (fig 1). At the time of diagnosis 156 children (83%) were less than 2 years old. Of these, 116 (74%) have been verified according to the ESPGAN criteria so far (table). Only 10 of the 188 children (5%) were more than 7 years old. Between 1970 and 1977 only children less than 2 years old were diagnosed as having coeliac dis-

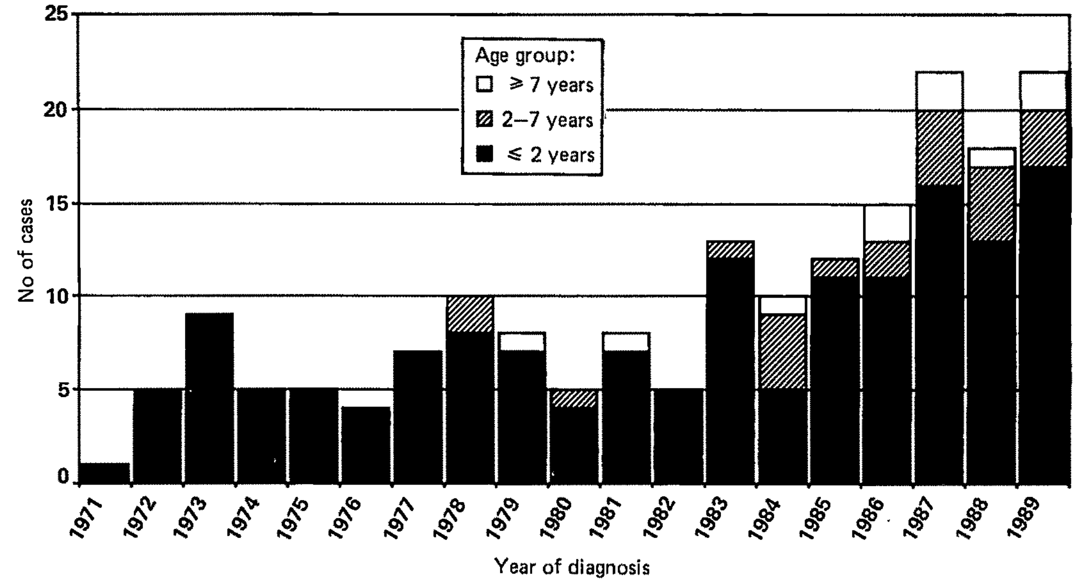


Figure 1 *New cases of coelic disease by age group and year of first small intestinal biopsy.*

Number of patients and cumulative incidence of coeliac disease at 2 years of age/1000 liveborn infants

Year of birth	*Total No*	*Verified according to ESPGAN criteria*	*Two small intestinal biopsy specimens taken*	*One small intestinal biopsy specimen taken*	*Cumulative incidence*
1970	2	2	0	0	0·31
1971	4	3	0	1	0·60
1972	9	8	0	1	1·44
1973	6	5	0	1	1·01
1974	4	4	0	0	0·67
1975	3	3	0	0	0·54
1976	8	7	0	1	1·53
1977	10	10	0	0	1·96
1978	5	5	0	0	1·02
1979	6	4	2	0	1·18
1980	5	3	1	1	0·99
1981	6	4	0	2	1·22
1982	8	8	0	0	1·57
1983	10	10	0	0	2·06
1984	8	7	0	1	1·54
1985	17	15	2	0	3·19
1986	14	9	2	3	2·58
1987	13	7	4	2	2·21
1988	18	2	6	10	2·93
Total	156	116	17	23	

ease. Not until 1979 was the diagnosis applied to children over 7 years of age (fig 1). Of the 188 patients, 131 (70%) were girls, which is significantly more than the expected number ($p<0{\cdot}001$). The preponderance of girls did not change during the period of investigation.

The cumulative incidence at 2 years of age for each birth cohort increased from 0·31/1000 liveborn infants in 1970 to 2·93/1000 in 1988 (table, fig 2). The last figure is a minimum, because not all children in the last cohort had reached the age of 2 years by the end of the study period. A linear regression was fitted to the data. The regression (b), that is the average yearly increase, was 0·12/1000/year ($p<0{\cdot}0001$, SE 0·02).

In the group in which coeliac disease had been diagnosed before the age of 2 years, the age at the onset of symptoms increased from a mean

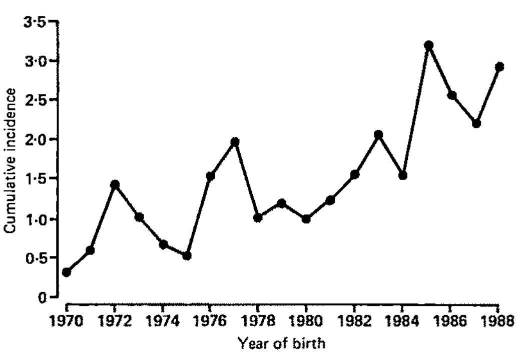


Figure 2 *Cumulative incidence of coelic disease at 2 years of age/1000 liveborn infants by birth cohort.*

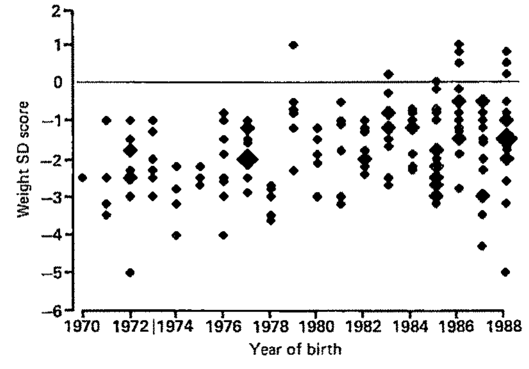


Figure 3 *Weight attained at the time of first small intestinal biopsy in children with coeliac disease <2 years of age related to their birth year.*

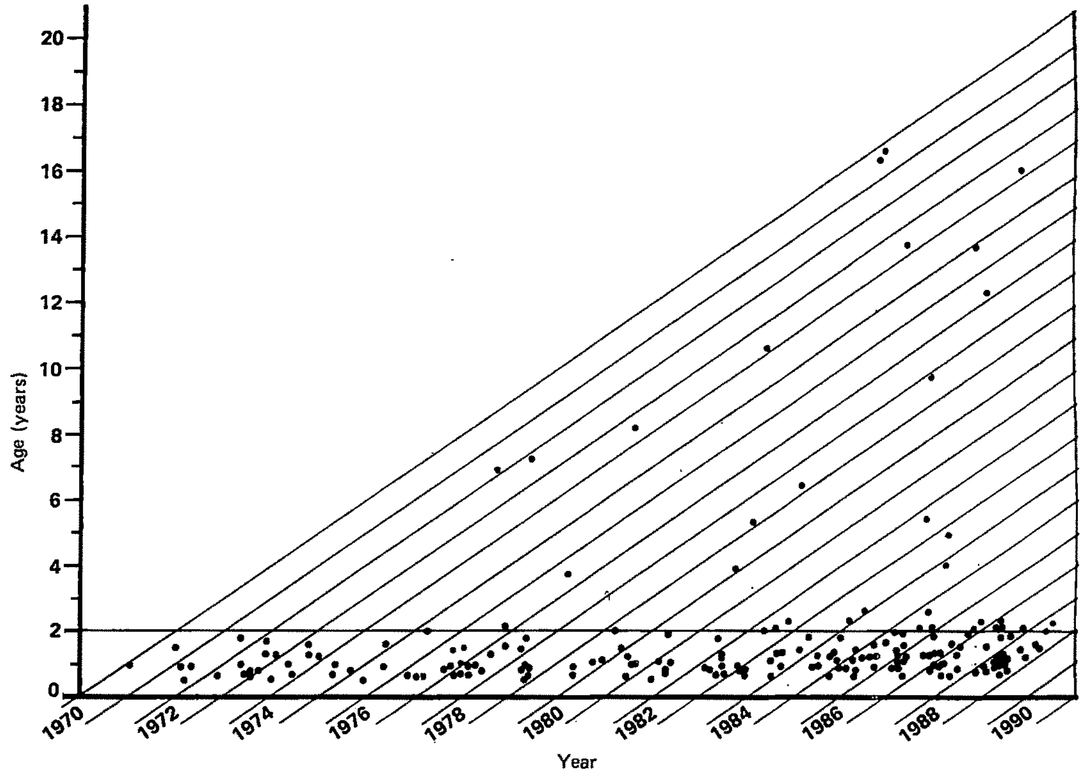


Figure 4 Age at diagnosis of coelic disease related to birth cohort (fields within oblique lines) and year of diagnosis. Solid circles indicate patients with coelic disease.

of 6·7 months in the first half of the observation period to 8·2 months in the second half ($p<0·0004$, $b=0·17$, SE 0·05).

The age at diagnosis increased from a mean of 12·4 months in the first half of the observation period to 13·4 in the last five months ($p<0·05$, $b=0·14$, SE 0·07). The mean time between onset and diagnosis did not change significantly, being 5·3 months for the whole period.

Weight at the time of diagnosis among children with coeliac disease diagnosed before the age of 2 years was generally far below the reference mean (fig 3). When a linear regression was fitted to the data, a slight but significant increase was found ($p=0·0001$, $b=0·06$, SE 0·02), but variations in weight increased during the second half of the 1980s.

Discussion

We have retrospectively studied the incidence of coeliac disease in birth cohorts born in Göteborg from 1970 to 1988, and found a threefold increase over the period. Of the 188 children studied, 83% were less than 2 years old at the time of the first small intestinal biopsy.

The first Swedish studies of children using the same diagnostic criteria as we used showed an incidence of between 1·02 and 1·16/1000 liveborn infants.[14 15] Later reports showed that the incidence was unchanged.[16–18] In another Swedish study 1866 healthy blood donors were tested with antigliadin antibodies and those with increased titres were offered a small intestinal biopsy.[19] An incidence of coeliac disease of 3·7/1000 was found.

In other parts of Europe, coeliac disease was reported to be increasing until the middle of the 1970s.[1 4 5 7 20 21] This was probably the result of a more active diagnostic approach, particularly the increased use of small intestinal biopsy in clinical practice. Since the second half of the 1970s, only decreasing[1–6] or unchanged[7 8] incidences have been reported, and the figures have varied among populations. Some differences are the result of varying diagnostic criteria, and others of the lack of standardised epidemiological approaches with subsequent difficulties in comparison. Some studies were based on figures without relation to a population.[4 22]

One important problem of longitudinal epidemiological studies is that of the duration of observation periods of the different birth cohorts (fig 4). To avoid a systematic error with overestimation of the incidence in the older cohorts, it is necessary to maintain the same observation time. A choice must be made between a shorter observation time that will exclude the cases that were diagnosed later, and a longer observation time resulting in a long delay before changes can be identified.

Another problem arises when the total population is divided by the number of cases. The cases must be derived from the birth cohorts which constitute the population at risk. In this study children from the surrounding areas treated in the department, and children who had moved to Göteborg before or after the diagnosis was made, were excluded. Children with coeliac disease who were born in Göteborg but in whom the diagnosis was made after they had moved away from the city were impossible to trace and therefore could not be included in the study. Consequently our cumulative incidence represents a minimum. The number of liveborn children in Göteborg varied between 4845 and 6694/year during the study period.

The migration of the population is yet

another problem in epidemiological studies. The inward migration of cases and population was well controlled in this study. The occurrence of coeliac disease in the population is not likely to differ between the part of the population that stays and the one that migrates out of the city. As we divided the number of cases into the number of liveborn infants, however, and not into the actual number of the cohort who lived in Göteborg, there will be a systematic error that will increase with migration out of the city related to a longer observation time. The number of children with coeliac disease within the birth cohort but in whom the disease was diagnosed after they had moved away from the city will also add to the systematic error with the observation time. There are two ways to adjust for these processes: one is to use a 'life-table' approach, in which the lost part of the cohort is subtracted and the cases are divided into the 'true' denominator. The other approach is to include only the cases in which coeliac disease was diagnosed during a short observation time, for example before 2 years of age, as was done in this study (fig 4). With the last method the problems will be considerably reduced.

Our study is the first to our knowledge to report an increasing incidence in coeliac disease since the beginning of the 1970s. The incidence is one of the highest ever reported, and even higher than those reported from Galway, Ireland 1960–70[23] and from Austria 1969–72,[24] making coeliac disease one of the most common of the chronic diseases in Swedish children today.

In the last cohorts a lower proportion of cases have fulfilled the ESPGAN criteria so far. This could not explain the observed increase, however, because the number with transient gluten intolerance is low and has been decreasing in our area, as in other parts of Sweden.[18] In addition, all doubtful cases were excluded from the study.

The increase could consequently not be explained by systematic errors or shortcomings in the methods used. Could it be the result of improved detection? Throughout the study, the same diagnostic criteria were used, and the biopsy specimens were examined by the same two pathologists. The ability to detect and interpret deviations in growth velocity, however, is thought to have improved among physicians and nurses at child health centres. Screening tests for antigliadin antibodies have been in clinical use in the area since the beginning of the 1980s. There is also an increasing awareness of the existence of coeliac disease both among medical staff and the general public. Consequently there has been an increase in the number of small intestinal biopsies done in the department during the study period, and the weight for age at diagnosis has slightly increased (fig 3). All these factors support improved detection as an explanation for the increased incidence. On the other hand, the cases with high weight SD scores could only explain part of the increase (fig 3) and the delay between the onset of symptoms and diagnosis did not change significantly. We also doubt that a different rate of detection could be the sole reason for the different incidence trends in different countries. This indicates that detection bias could only partly explain the observed increase.

We have found a threefold increase in the incidence of coeliac disease over the last 20 years. Our data indicate that only a small part of this increase may be explained by increased diagnostic activities or improved clinical detection or screening. Other factors that may influence the incidence of coeliac disease, such as feeding patterns and gluten consumption, are currently being investigated.

The study was supported by grants from the Göteborg Medical Society, Gothenburg University, the First of May Flower Annual Campaign for Children's Health, and the Wilhelm and Martina Lundgren Foundation.

1 Littlewood JM, Crollick AJ, Richards IDG. Childhood coeliac disease is disappearing. *Lancet* 1980;**ii**:1359.
2 Challacombe DN, Baylis JM. Childhood coeliac disease is disappearing. *Lancet* 1980;**ii**:1360.
3 Dossetor JFB, Gibson AAM, McNeish AS. Childhood coeliac disease is disappearing. *Lancet* 1981;**i**:322–3.
4 Langman MJS, McConnell TH, Spiegelhalter DJ, McConnell RB. Changing patterns of coeliac disease frequency: an analysis of coeliac society membership records. *Gut* 1985;**26**:175–8.
5 Logan RFA, Rifkind EA, Busuttil A, Gilmour HM, Ferguson A. Prevalence and 'incidence' of celiac disease in Edinburgh and the Lothian region of Scotland. *Gastroenterology* 1986;**90**:334–42.
6 Stevens FM, Egan-Mitchell B, Cryan E, McCarthy CF, McNicholl B. Decreasing incidence of coeliac disease. *Arch Dis Child* 1987;**62**:465–8.
7 Greco L, Tozzi AE, Mayer M, Grimaldi M, Silano G, Auricchio S. Unchanging clinical picture of coeliac disease presentation in Campania, Italy. *Eur J Pediatr* 1989;**148**: 610–3.
8 Mäki M, Kallonen K, Lähdeaho M-L, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. *Acta Paediatr Scand* 1988;**77**:408–12.
9 Official Report. *Public health in Sweden 1977.* Stockholm: National Board of Health and Welfare, 1979.
10 Meeuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461–3.
11 McNeish AS, Harms HK, Rey J, Shmerling DH, Visakorpi JK, Walker-Smith JA. The diagnosis of coeliac disease: a commentary on the current practices of the members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN). *Arch Dis Child* 1979;**54**:783–6.
12 Fällström SP, Kristiansson B, Ryd W. Histological studies of small intestinal biopsies from infants with low rate of weight gain. *Acta Pathologica et Microbiologica Scandinavica, section A* 1981;**89**:431–8.
13 Kristiansson B, Karlberg J, Fällström SP. Infants with low rate of weight gain. I. A study of organic factors and growth patterns. *Acta Paediatr Scand* 1981;**70**:655–62.
14 Berg NO, Lindberg T. Incidence of coeliac disease and transient gluten intolerance in children in a Swedish urban community. *Acta Paediatr Scand* 1979;**68**:397–400.
15 Stenhammar L, Johansson C-G. The incidence of coeliac disease in children in south-east Sweden. *Acta Paediatr Scand* 1981;**70**:379–81.
16 Stenhammar L, Ansved P, Jansson G, Jansson U. The incidence of childhood celiac disease in Sweden. *J Pediatr Gastroenterol Nutr* 1987;**6**:707–9.
17 Lindberg T. Coelic disease and infant feeding practices. *Lancet* 1981;**i**:449.
18 Stenhammar L, Ansved P, Jansson G, Jansson U. Incidences of childhood coeliac disease and transient gluten intolerance move discrepantly in UK and Sweden. *Arch Dis Child* 1987; **62**:1089.
19 Hed J, Lieden G, Ottosson E, *et al.* IgA anti-gliadin antibodies and jejunal mucosal lesions in healthy blood donors. *Lancet* 1986;**ii**:215.
20 Kokkonen J, Similä S, Vuolukka P. The incidence of coeliac disease and pyloric stenosis in children in northern Finland. *Ann Clin Res* 1982;**14**:123–8.
21 Van Stirum J, Baerlocher K, Fanconi A, Gugler E, Shmerling DH. The incidence of coeliac disease in children in Switzerland. *Helv Paediatr Acta* 1982;**37**:421–30.
22 Kelly DA, Phillips AD, Elliott EJ, Dias JA, Walker-Smith JA. Rise and fall of coeliac disease 1960–85. *Arch Dis Child* 1989;**64**:1157–60.
23 Mylotte M, Egan-Mitchell B, McCarthy CF, McNicholl B. Incidence of coeliac disease in the west of Ireland. *BMJ* 1973;**i**:703–5.
24 Rossipal E. Häufigkeit der Cöliakie im Einzugsgebiet der Kinderklinik Graz. *Zeitschrift fur Kinderheilkunde* 1975;**119**: 143–9.

Archives of Disease in Childhood 1991; 66: 612–616

Glucose tolerance in cystic fibrosis

Susanne Lanng, Birger Thorsteinsson, Gunna Erichsen, Jørn Nerup, Christian Koch

**Danish Cystic
Fibrosis Centre,
Department of
Paediatrics,
Rigshospitalet,
Blegdamsvej 9,
DK-2100 Copenhagen Ø,
Denmark**
Susanne Lanng
Gunna Erichsen
Christian Koch

**Department of
Internal Medicine C,
Bispebjerg Hospital,
Copenhagen,
Denmark**
Birger Thorsteinsson

**Steno Memorial Hospital,
Gentofte, Copenhagen**
Jørn Nerup

Correspondence to:
Dr Lanng.

Accepted 16 January 1991

Abstract

Glucose tolerance was evaluated in 356 living and dead patients with cystic fibrosis who were recorded at the Danish Cystic Fibrosis Centre. Twenty two patients (6%) were treated elsewhere, 25 (7%) were unable, unwilling or too young (age <2 years) to participate; 309 patients (87%) were therefore eligible for the study of whom 99 (32%) were dead and 210 (68%) were alive. Of the dead patients, 13 also had diabetes mellitus (13%). Of the living patients (median age 14 years, range 2–40), nine (4%) were known to have diabetes and all were being treated with insulin. In the remaining 201 patients an oral glucose tolerance test (1·75 g/kg body weight, maximum 75 g) was carried out. A total of 155 patients (74%) had normal glucose tolerance, 31 (15%) had impaired glucose tolerance, and 15 (7%) had diabetes mellitus according to the WHO criteria. The percentage of glycated haemoglobin (HbA_{1c}) (reference range 4·1–6·4%) increased significantly as glucose tolerance decreased: when glucose tolerance was normal the median was 5·2%; when it was impaired the figure was 5·5%; in patients whose diabetes was diagnosed by the oral glucose tolerance test it was 5·9%; and in patients already known to have diabetes mellitus it was 8·6%. The incidence and prevalence of impaired glucose tolerance and diabetes mellitus increased with age. From the age of 15 to 30 years the decrease in the prevalence of normal glucose tolerance was almost linear. Within this age span the proportion of patients with cystic fibrosis with normal glucose tolerance was reduced by roughly 5%/year. Only 35% (95% confidence interval (CI) 22 to 48%) of the patients with cystic fibrosis who were alive at the age of 25 years had normal glucose tolerance; 32% (95% CI 14 to 49%) were diabetic.

The prevalence of glucose intolerance in cystic fibrosis is rapidly increasing with age; its potentially harmful effect on the prognosis of cystic fibrosis is of increasing importance as the length of survival of these patients increases.

Cystic fibrosis is an autosomal recessive disorder that affects many organs including the pancreas. In addition to insufficiency of pancreatic exocrine function, there is a high incidence of pancreatic endocrine dysfunction. Early studies described glucose tolerance in the disease,[1 2] but an association between diabetes mellitus and cystic fibrosis was recognised in 1955.[3] Since then many investigators have reported glucose intolerance and diabetes mellitus as common problems in cystic fibrosis.[4–23]

The prevalence of glucose intolerance in cystic fibrosis increases with age,[5] and because of the increased life expectancy of patients with cystic fibrosis,[24 25] the possible adverse effect of glucose intolerance on prognosis has become increasingly relevant in recent years.[26] Previous studies have included only a limited number of patients, often highly selected, and have applied various diagnostic criteria of glucose intolerance. We therefore studied the prevalence of impaired glucose tolerance and diabetes mellitus (WHO criteria) in a large group of unselected patients followed up at the Danish Cystic Fibrosis Centre.

Subjects and methods

Since the foundation of the Danish Cystic Fibrosis Centre in 1949, 356 patients (181 men) have been followed up at the centre. The diagnosis of cystic fibrosis was based on the presence of abnormal electrolyte concentrations in sweat and a typical clinical picture.[27 28] By October 1989, 99 patients (50 men) had died, and 22 (12 men) had been treated elsewhere. From the records of the dead patients, information was obtained about sex, age at death, family history of diabetes, presence or absence of diabetes mellitus (diagnosed by raised blood glucose concentration or glycosuria, or both), and, if they were diabetic, the age at the time of diagnosis of the diabetes.

Of the 235 patients (119 men) currently attending the clinic regularly, 210 (89%) patients (104 men) were willing to participate in the study. Reasons given for not taking part were: unwillingness (n=9), inability because of mental disease (n=3), and age less than 2 years (n=13), which was the minimal age for inclusion. The median age of the 210 patients was 14 years (range 2–40), median height 152 cm (range 81–190), and median weight 40 kg (range 10–84). One hundred and twenty three patients had chronic infections with *Pseudomonas aeruginosa*.

We recommend a normal balanced diet for our patients preferably one with a high energy content. We did not give nutrients or fluids either parenterally or by nasogastric tube.

Nine of the 210 patients were known to have diabetes mellitus (4%); all were being treated with insulin. The remaining 201 patients (99 men) underwent an oral glucose tolerance test according to the WHO recommendations.[29] Briefly, after an overnight fast the patient was given 1·75 g glucose monohydrate/kg body weight (maximum 75 g), dissolved in 2–300 ml of lemon flavoured water, over 3–4 minutes. Capillary plasma glucose concentrations were measured before, and 60 and 120 minutes after, the glucose load. During the study the patient was resting, fasting, and did not smoke.

After completion of the glucose tolerance test, blood was sampled for estimation of glycated haemoglobin (HbA_{1c}), assessment of measures of liver function, and presence of *P aeruginosa* precipitins. A pulmonary function test was done for all patients over 6 years old. Finally, the patient (or the relatives) was asked about the daily number of pancreatic enzyme capsules taken (used as a measure of the exocrine pancreatic function), the family history of diabetes, and the use of any drugs with a potential for influencing glucose tolerance.

The capillary plasma glucose concentration was measured with a glucose dehydrogenase method (Merck).[30] According to the WHO criteria,[29] a capillary plasma glucose concentration of 8·8 mmol/l or less at two hours was considered as normal glucose tolerance, a value of 8·9–12·1 mmol/l indicated impaired glucose tolerance, and a value of 12·2 mmol/l or more was diagnostic of diabetes mellitus.

HbA_{1c} was measured as previously described[31]; the reference range is 4·1–6·4%. Precipitins against *P aeruginosa* were measured by Høiby's method.[32]

Pulmonary function was assessed by forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), and recorded on an electronic spirometer (Spiroton, Draeger). The results are expressed as percentages of the reference values for sex and height in patients less than 20 years old[33] and sex, height, and age in patients aged 20 years or more.[34]

The study was conducted in accordance with the Declaration of Helsinki (Tokyo revision) and was approved by the municipal medical ethics committee of Copenhagen and Frederiksberg. Informed consent was obtained from all participants or their parents, or both.

The statistical evaluation includes nonparametric tests (Kruskal-Wallis test, Mann-Whitney test, Fisher's exact test) and life table analysis; a probability of less than 0·05 (two-tailed) was accepted as significant, and 95% confidence intervals (CI) were calculated. Data are presented as median (ranges) unless otherwise stated.

Results

Thirteen of the 99 dead patients had had diabetes mellitus (13%); five had been treated with insulin. In 74 patients (75%) diabetes mellitus had not been diagnosed, and in 12 patients (12%) it was not possible to establish whether they had been diabetic or not. Diabetes mellitus was diagnosed at the median age of 16 years (range 6–32). Four patients had been diabetic for a median of 4 years (range 3–13) before death (two were treated with insulin), whereas nine became diabetic within their last year, including four in whom glycosuria was a terminal event. The median age of the diabetic patients was 23 years (range 6–33) at the time of death. There was a family history of diabetes mellitus in eight cases, two of whom were diabetic themselves.

Glucose intolerance was found in 55 of the 210 who were still alive (26%), including 24 with diabetes mellitus (11%). The latter prevalence does not differ from the prevalence of 13% among the dead patients (p=0·80).

HbA_{1c} increased significantly as glucose tolerance decreased (table). In patients with normal or impaired glucose tolerance and with diabetes mellitus diagnosed by glucose tolerance test, the percentages of HbA_{1c} were, however, within or close to the reference range, and the ranges of HbA_{1c} values overlapped between groups though to a lesser extent for known diabetes mellitus.

In the patients known to have diabetes, it had been diagnosed at a median age of 15 years (range 3–24). This is no different from the median age at diagnosis (16 years) in the 13 deceased patients with diabetes (p=0·46). Only two patients developed diabetes before the age of 10 years (at the ages of 3 and 8 years, respectively). They both presented with ketonuria and

Characteristics of endocrine and exocrine pancreatic function and pulmonary function in 210 patients with cystic fibrosis classified according to WHO criteria of glucose tolerance. Data for FEV_1 and FVC measurements are taken from 115 patients with normal glucose tolerance and 28 with impaired glucose tolerance, all more than 6 years old. Figures are median (range) except where otherwise stated

	Normal glucose tolerance	*Impaired glucose tolerance*	*Diabetes mellitus*		
			Diagnosed by oral glucose tolerance test	*Known cases*	*Total*
No (%) of patients	155 (74)	31 (15)	15 (7)	9 (4)	24 (11)
Age (years)	11·4 (2–38)	18·3 (4–28)*	22·0 (14–40)*§	20·0 (14–28)*	21·5 (14–40)*§
Plasma glucose concentration (mmol/l):					
Fasting	5·3 (3·8–6·8)	5·3 (3·9–6·9)	5·7 (4·2–8·0)†	Not known	Not known
After one hour	10·0 (5·3–16·0)	11·5 (8·7–17·4)*	15·4 (10·5–21·0)*‡	Not known	Not known
After two hours	6·4 (2·5–8·8)	10·3 (8·9–12·0)	14·6 (12·4–21·0)	Not known	Not known
HbA_{1c} (%)	5·2 (4·1–6·2)	5·5 (4·4–6·3)*	5·9 (5·2–7·0)*§	8·6 (5·7–11·8)*‡‖	6·4 (5·2–11·8)*‡‖
FEV_1 (% of normal)	77 (16–128)	61 (27–121)†	59 (25–100)	39 (26–92)*	52 (25–110)*
FVC (% of normal)	89 (34–150)	84 (44–123)	75 (45–126)	57 (28–101)*§¶	72 (28–126)†
No of precipitins against *P aeruginosa*	1·2 (0–46)	21 (0–45)*	30 (0–44)*	28 (0–44)†	30 (0–44)*
No of capsules/day pancreatic enzymes	30 (0–195)	30 (0–135)	21 (0–44)*§	36 (12–110)¶	24 (0–110)

Compared with normal glucose tolerance: *p<0·01; †p<0·05.
Compared with impaired glucose tolerance: ‡p<0·01; §p<0·05.
Compared with diabetes diagnosed by oral glucose tolerance test: ‖p<0·01; ¶p<0·05.

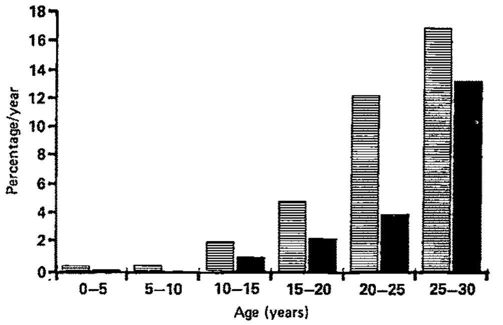


Figure 1 Annual percentage of patients with cystic fibrosis whose glucose tolerance deteriorated from normal to impaired glucose tolerance or diabetes mellitus (hatched columns), and from normal or impaired glucose tolerance to diabetes mellitus (solid columns) plotted against age.

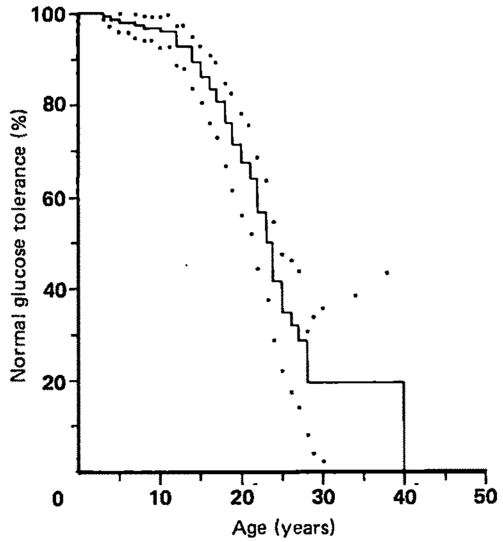


Figure 2 Percentage of patients with cystic fibrosis and normal glucose tolerance plotted against age in a life table. The dots indicate 95% CI.

have needed insulin ever since, making the coincidence of cystic fibrosis and insulin dependent (type 1) diabetes mellitus likely.

A total of eight patients were receiving corticosteroids at the time of the study. In three diabetic patients (two with known diabetes and one who had been diagnosed after a glucose tolerance test), the onset of diabetes was preceded by prednisone treatment for allergic bronchopulmonary aspergillosis for 22 months, four months, and less than one month, respectively; a fourth patient, diagnosed by glucose tolerance test and diabetic for one year, had to start insulin injections after prednisone treatment of aspergillosis lasting two months. Another four patients treated with prednisone for aspergillosis did not develop diabetes. No patient received thiazides.

The median age of the patients in the different classes of glucose tolerance increased as glucose tolerance decreased (table), but the age of the patients in the two classes of diabetes mellitus (those diagnosed by glucose tolerance test and those already known) did not differ significantly. Two of the 117 patients who were less than 15 years of age (2%) were diabetic compared with 22 of 93 patients aged 15 years or more (24%; p<0·01).

By life table analysis we estimated the incidence and prevalence of different classes of glucose intolerance. The annual incidences of patients deteriorating from normal to impaired glucose tolerance or diabetes mellitus, and from normal or impaired glucose tolerance to diabetes mellitus, calculated for five year age groups, both steadily increased over the age of 10 years (fig 1). In the age group 10–15 years the rate of deterioration from impaired glucose tolerance to diabetes mellitus is about 2%/year, increasing to about 17%/year in the age group 25–30 years; in parallel, the incidence of diabetes mellitus increases from about 1 to 13%/year in the same age groups.

The prevalence of normal glucose tolerance decreases with age (fig 2); from the age of 15 to 30 years the decrease is almost linear. Within this age group the proportion of patients with normal glucose tolerance is reduced by roughly 5%/year. Thus, 86% (95% CI 80 to 93%) of the patients have normal glucose tolerance at the age of 15 years, whereas only 35% (95% CI 22 to 48%) have normal glucose tolerance at the age of 25; at the latter age 32% (95% CI 14 to 49%) are diabetic.

Twenty one patients gave a family history of diabetes (including two pairs of siblings). Four (19%) of these patients had diabetes (two were being treated with insulin) compared with 20 (11%) of the 189 patients who did not give a family history of diabetes (p=0·25).

Median FEV_1 was lower in patients with impaired glucose tolerance or known diabetes mellitus, and in all diabetic patients compared with those with normal glucose tolerance, whereas the differences between the normal group and those diagnosed by glucose tolerance test, and the impaired group and the known diabetic group were not significant (both p<0·10) (table). FVC was lower in patients known to have diabetes than in all other groups, and lower in diabetic patients than in patients with normal glucose tolerance (table). Precipitins against *P aeruginosa* were lower in patients with normal glucose tolerance than in all other groups (table). The daily intake of pancreas enzyme capsules was lower in patients with diabetes diagnosed by glucose tolerance test than in all other groups (table).

Discussion

This first large cross sectional study of oral glucose tolerance in unselected patients with cystic fibrosis over the age of 2 years confirms that the prevalence of glucose intolerance (26%) in cystic fibrosis is high. For comparison, in 12 studies comprising a total of 284 patients an oral glucose tolerance test identified 21–75% of the patients as being glucose intolerant (the mean was 41%, but varying criteria for glucose tolerance and diabetes mellitus were used).[4 5 7 9 10 13–16 18 20 21]

Eleven per cent of our patients were diabetic; the retrospective part of our study showed an almost similar prevalence of diabetes mellitus in the dead patients. Seventeen studies, in which various criteria for selection and diagnosis were applied, included a total of 1510 patients of various ages.[2 4–8 11 12 14 16–23] Of these patients, 134 (8·9%, range 0–17%) were diabetic. The mean prevalence of diabetes mellitus calculated from these studies was apparently the same (7–9%), whether an oral glucose tolerance test (n=266),[2 4 5 7 14 16 18 20 21] random blood glucose values (n=448[22]), the presence of glycosuria (n=221[6 8 11 12]), or non-stated diagnostic procedures (n=575[17 19 23]) were used for diagnosis.

Impaired glucose tolerance, which in some populations is said to accompany a greater risk of developing arterial disease than normal glucose tolerance,[29] was found in 15% of our patients. In seven other studies, again with varying criteria for the diagnosis of impaired glucose tolerance, the mean prevalence was 30% (n=201, range 18–56%).[5 7 13 15 17 19 20]

The prevalence of diabetes mellitus reported here is therefore higher, though those of impaired glucose tolerance and both types of glucose intolerance considered together are lower than found previously. No obvious explanations exist for this discrepancy. The influence of differences between the patient groups in age or other selection criteria or from varying diagnostic criteria for the different classes of glucose tolerance may be of importance. It is, however, beyond any doubt that the incidence and prevalence of glucose intolerance—impaired glucose tolerance as well as diabetes mellitus—is much higher in patients with cystic fibrosis than in any other age matched group.

It is not known whether glucose intolerance influences the prognosis of cystic fibrosis. Progressive clinical deterioration in patients with cystic fibrosis and diabetes mellitus has been reported by some investigators,[5 22] but was not detected by others.[7 13 18 20] We observed that FEV_1 decreased as glucose tolerance decreased, as did FVC, and there were more precipitins against *P aeruginosa* found in patients with all classes of glucose intolerance compared with normals. It is doubtful, however, whether these findings reflect a causal relationship between glucose intolerance and cystic fibrosis in general, but merely the difference in age (equal to the duration of cystic fibrosis) between the different groups of glucose tolerance. The daily intake of pancreatic enzyme—a rough estimate of exocrine pancreatic function—was for unknown reasons lower in patients with diabetes diagnosed by glucose tolerance test than in all other patients. Using more up to date techniques, a parallel loss of exocrine and endocrine pancreatic function has been shown.[14]

Although diabetes mellitus in cystic fibrosis is generally considered mild in itself,[5 10 12] no data exist to substantiate the statement. The development of the late diabetic complications, however, as are seen in other states of diabetes mellitus like insulin dependent diabetes mellitus and non-insulin dependent (type 2) diabetes mellitus, has only been described in a few patients with both cystic fibrosis and diabetes mellitus.[18 35–37]

Until reliable studies confirm the 'mild' nature of the glucose intolerance in cystic fibrosis, both in itself and in its effect on the prognosis, we feel that diabetes mellitus in cystic fibrosis should be treated as carefully as diabetes mellitus of all types is treated in younger subjects. The question then arises of how to identify the patients with cystic fibrosis and glucose intolerance.

Clinical diagnosis prompted by symptoms of hyperglycaemia seems unreliable, as many diabetic patients are asymptomatic, including our own group of patients who were diagnosed by oral glucose tolerance test. The reliability of regular urine testing for glucose has not been systematically evaluated in patients with cystic fibrosis. According to the WHO recommendations,[29] the fasting blood glucose concentration alone should be considered less reliable as true fasting cannot be assured, which may lead to the false diagnosis of diabetes mellitus. If it is used, some diabetic patients will remain undiagnosed; in our study 87% of the 15 patients with diabetes mellitus diagnosed by oral glucose tolerance testing had fasting capillary plasma glucose values below the diagnostic value of 7·8 mmol/l.[29] Finally, measurement of HbA_{1c} has been suggested as a screening procedure.[13 20] In our study, however, 73% of the patients diagnosed by oral glucose tolerance test had HbA_{1c} values within the reference range. In contrast to Stutchfield *et al*, we found a HbA_{1c} value above the reference range diagnostic of diabetes mellitus.[20] Serial determination of HbA_{1c} values has been suggested for the detection of impairment of glucose tolerance,[13 20] but its value remains to be established.[22]

We have demonstrated that oral glucose tolerance tests are reliable in the detection of diabetes mellitus in patients with cystic fibrosis. We intend to review our patients over the age of 2 years annually to determine the ages and intervals at which it would be reasonable to recommend oral glucose tolerance tests as part of clinical practice. At present, we hypothesise that only patients over the age of 10 years will need regular tests, as our two patients who developed diabetes mellitus below this age limit both had frank symptoms of diabetes at onset.

We are grateful to Nurse Annelise Hansen at the cystic fibrosis outpatient clinic 5002, Rigshospitalet, for excellent technical assistance.

1 Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* 1938;**56**:344–99.
2 Lowe CU, May CD, Reed SC. Fibrosis of the pancreas in infants and children. *Am J Dis Child* 1949;**78**:349–74.
3 Shwachman H, Leubner H, Catzel P. Mucoviscidosis. *Adv Pediatr* 1955;**7**:249–323.
4 Rosan RC, Shwachman H, Kulczycki LL. Diabetes mellitus and cystic fibrosis of the pancreas. *Am J Dis Child* 1962; **104**:625–34.
5 Handwerger S, Roth J, Gorden P, Di Sant'Agnese P, Carpenter DF, Peter G. Glucose intolerance in cystic fibrosis. *N Engl J Med* 1969;**281**:451–61.
6 Gracey M, Anderson CM. Cystic fibrosis of the pancreas in adolescents and adulthood. *Australasian Annals of Medicine* 1969;**18**:91–101.
7 Milner AD. Blood glucose and serum insulin levels on children with cystic fibrosis. *Arch Dis Child* 1969;**44**:351–5.
8 Mitchell-Heggs P, Mearns M, Batten JC. Cystic fibrosis in adolescents and adults. *Q J Med* 1976;**45**:479–504.
9 Wilmshurst EG, Soeldner JS, Holsclaw DS, *et al.* Endogenous and exogenous insulin responses in patients with cystic fibrosis. *Pediatrics* 1975;**55**:75–82.
10 Lippe BM, Sperling MA, Dooley RR. Pancreatic alpha and beta cell functions in cystic fibrosis. *J Pediatr* 1977;**90**: 751–5.
11 Shwachman H, Kowalski M, Khaw KT. Cystic fibrosis: a new outlook. *Medicine* 1977;**56**:129–49.
12 Di Sant'Agnese PA, Davis PB. Cystic fibrosis in adults: 75 cases and a review of 232 cases in the literature. *Am J Med* 1979;**66**:121–32.

13 Bistritzer T, Sack J, Eshkol A, Katznelson D. Hemoglobin A_1 and pancreatic β cell function in cystic fibrosis. *Isr J Med Sci* 1983;**19**:600–3.

14 Geffner ME, Lippe BM, Kaplan SA, *et al.* Carbohydrate tolerance in cystic fibrosis is closely linked to pancreatic exocrine function. *Pediatr Res* 1984;**18**:1107–11.

15 Knöpfle G. Endokrine Pancreasfunktion bei Mukoviszidose. *Klin Pädiatr* 1985;**197**:13–20.

16 Mohan V, Alagapan V, Snehalatha C, Ramachandran A, Thiruvengadam KV, Viswanathan M. Insulin and C-peptide responses to glucose load in cystic fibrosis. *Diabete Metab* 1985;**1**:376–9.

17 Berkin KE, Alcock SR, Stack BH. Cystic fibrosis—a review of 26 adolescents and adult patients. *Eur J Respir Dis* 1985; **67**:103–11.

18 Rodman HM, Doershuk CF, Roland JM. The interaction of two diseases: diabetes mellitus and cystic fibrosis. *Medicine* 1986;**65**:389–97.

19 Penketh ARL, Wise A, Mearns MB, Hodson ME, Batten JC. Cystic fibrosis in adolescents and adults. *Thorax* 1987;**42**: 526–32.

20 Stutchfield PR, O'Halloran S, Teale JD, Isherwood D, Smith CS, Heaf D. Glycosylated haemoglobin and glucose intolerance in cystic fibrosis. *Arch Dis Child* 1987;**62**: 805–10.

21 Hartling SG, Garne S, Binder C, *et al.* Proinsulin, insulin, and C-peptide in cystic fibrosis after an oral glucose tolerance test. *Diabetes Res* 1988;**7**:165–9.

22 Finkelstein SM, Wielinski CL, Elliott GR, *et al.* Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;**112**: 373–7.

23 Nagel RA, Westaby D, Javaid A, *et al.* Liver disease and bileduct abnormalities in adults with cystic fibrosis. *Lancet* 1989;**ii**:1422–5.

24 Nielsen OH, Schiøtz PO. Cystic fibrosis in Denmark in the period 1945–1981: evaluation of centralized treatment. *Acta Paediatr Scand* 1982;**71**(suppl 301):107–19.

25 Szaff M, Høiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection. *Acta Paediatr Scand* 1983;**72**:651–7.

26 Knowles MR, Fernald GW. Diabetes and cystic fibrosis: new questions emerging from increased longevity. *J Pediatr* 1988;**112**:415–6.

27 Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959;**23**:545–9.

28 Nielsen OH, Flensborg EW. Sweat electrolyte investigation by Gibson and Cooke's pilocarpine iontophoresis method. *Ugeskr Laeger* 1981;**143**:2302–6.

29 WHO Study Group. Diabetes mellitus. *WHO Tech Rep Ser* 1985;**727**:1–113.

30 Banauch D, Brümmer W, Ebeling W, *et al.* A glucose dehydrogenase for the determination of glucose concentration in body fluids. *Zeitschrift fur Klinische Chemie und Klinische Biochemie* 1975;**13**:101–7.

31 Svendsen PAa, Lauritzen T, Søegaard U, Nerup J. Glycosylated haemoglobin and steady state mean blood glucose concentration in type 1 (insulin-dependent) diabetes. *Diabetologia* 1982;**23**:403–5.

32 Høiby N. Pseudomonas aeruginosa infection in cystic fibrosis. Diagnostic and prognostic significance of Pseudomonas aeruginosa precipitins determined by means of crossed immunoelectroforesis. A survey. *Acta Pathologica et Microbiologica Scandinavica. Section C, Immunology* 1977;**85** (suppl 262):3–96.

33 Cotes JE. *Lung function. Assessment and application in medicine.* Oxford: Blackwell Scientific, 1979:340.

34 Quanjer PhH, Dalhuijsen A, van Zomeren BC. Clinical respiratory physiology: summary of reference values. *Bull Eur Physiopathol Respir* 1983;**19**(suppl 5):45–51.

35 Dolan TF. Microangiopathy in a young adult with cystic fibrosis and diabetes mellitus. *N Engl J Med* 1986;**314**: 991–2.

36 Allen JL. Progressive nephropathy in a patient with cystic fibrosis and diabetes. *N Engl J Med* 1986;**315**:764.

37 Sullivan MM, Denning CR. Diabetic microangiopathy in patients with cystic fibrosis. *Pediatrics* 1989;**84**:642–7.

Insect stings

Children who are stung by insects do better on the whole than adults in that they are less likely to have severe or life threatening reactions. Recent work from the Johns Hopkins Medical School has provided information about the use of desensiting injections (Valentine MD *et al*, *New England Journal of Medicine* 1990;**323**:1601–3). A total of 242 children aged from 2 to 16 years had had a generalised reaction confined to the skin after an insect bite or sting and had positive skins tests with one or more of five insect venoms. Sixty eight of the children were given a series of desensitising injections using the appropriate venom. On follow up about half of all the children were stung again. In the treated group 1·2% of subsequent stings gave rise to systemic reactions but 9·2% did so in the untreated children. None of the reactions was serious.

The authors conclude that immunotherapy is effective in preventing systemic reactions after subsequent stings but that, as such reactions are almost always fairly mild, the treatment is not usually necessary. The study does not show whether immunotherapy would prevent severe reactions but such a study will probably never be done as it is calculated that it would need 17 000 patient years in both treated and untreated groups. An editorial in the same issue recommends treating all adults with a systemic reaction and children who have had a severe reaction (laryngeal oedema, asthma, or anaphylactic shock).[1] If treatment is offered it should be with venom and not with whole body extracts which are deemed 'practically inert'.[2]

ARCHIVIST

1 Lockey RF. Immunotherapy for allergy to insect stings [Editorial]. *N Engl J Med* 1990;**323**:1627–8.

2 Reynolds JEF, ed. *Martindale. The extra pharmacopoeia.* 29th Ed. London: The Pharmaceutical Press, 1989:464.

Archives of Disease in Childhood 1991; **66**: 617–622

Mechanisms of gastro-oesophageal reflux in cystic fibrosis

S Cucchiara, F Santamaria, M R Andreotti, R Minella, P Ercolini, V Oggero, G de Ritis

Abstract
Abnormal degrees of gastro-oesophageal reflux (GOR) were detected by 24 hour intraoesophageal pH measurement in 12 of 14 children (mean age 7·9 years; range 5 months–16 years) affected by cystic fibrosis and complaining of symptoms suggesting GOR. These patients underwent combined recording of distal oesophageal motility and intraluminal pH in order to investigate mechanisms of GOR. Inappropriate lower oesophageal sphincter relaxation was the most common mechanism of reflux in all patients. Other mechanisms (appropriate relaxation or lowered pressure of the lower oesophageal sphincter, increased intragastric pressure) were detected less frequently. Frequency of inappropriate lower oesophageal sphincter relaxations was significantly higher in patients with cystic fibrosis than in other study groups (symptomatic GOR, GOR disease complicated by respiratory complaints). Inappropriate lower oesophageal sphincter relaxations occurred with the same frequency in patients with cystic fibrosis and in a group of children with GOR disease complicated by oesophagitis. Abnormalities of distal oesophageal contractions such as decreased amplitude or uncoordinated waves were also recorded in cystic fibrosis patients. Seven patients with cystic fibrosis completed a therapeutic trial for eight weeks consisting of postural treatment and oral cisapride, a new prokinetic drug. The oesophageal acid exposure improved in only three patients. We conclude that pathologic GOR is commonly asssociated with cystic fibrosis. The predominant reflux mechanism in these patients is a transient inappropriate lower oesophageal sphincter relaxation rather than a low steady state basal lower oesophageal sphincter pressure.

Department of Paediatrics,
2nd School of Medicine,
University of Naples,
Italy
S Cucchiara
F Santamaria
M R Andreotti
R Minella
P Ercolini
V Oggero
G de Ritis

Correspondence to:
Dr Salvatore Cucchiara,
Dipartimento di Pediatria,
II Facoltà di Medicina,
Via S Pansini 5,
80131 Napoli,
Italia.

Accepted 15 November 1990

Many studies have implied that gastro-oesophageal reflux (GOR) may be an important cause of respiratory disease either by pulmonary aspiration of refluxed gastric contents or by neurally mediated reflex bronchoconstriction secondary to irritation of oesophageal mucosa.[1–4] Nevertheless, establishing a direct association between reflux and pulmonary disease is difficult.[5] Recently, it has also been proposed that GOR may exacerbate pre-existing chronic respiratory disorders if the latter alter any of the antireflux barriers.[1 2] An association between GOR and cystic fibrosis has been reported in recent years and it has been suggested that aspiration of regurgitated gastric contents may worsen chronic pulmonary disease in these patients.[6–9]

The purposes of this study were to document the incidence of pathologic GOR in a group of patients with cystic fibrosis with symptoms suggesting GOR and to evaluate mechanisms responsible for reflux in the same patients.

Patients and methods

Fourteen patients with cystic fibrosis (mean age 7·9 years, range 5 months–16 years) and symptoms suggesting GOR such as heartburn, dysphagia, and regurgitation and/or vomiting underwent both prolonged intra-oesophageal pH monitoring and combined intraoesophageal manometric and pH recordings. All patients had mild to moderate respiratory disease. The mean Chrispin-Norman score on the last chest radiograph was 12 (range 4–21).[10] The forced expiratory volume in one second (FEV_1) was measured in five cooperative patients only and the values obtained expressed as per cent of the normal values for age and sex (mean 66·4%; range: 41·1–78·3%).

The therapeutic programme consisted of postural drainage, aerosol treatment with mucolytics and/or antibiotics, pancreatic enzymes, and vitamins. No bronchodilator drugs (β_2 agonists, theophylline) were prescribed.

Oesophageal pH was monitored for 24 hours with a 1·5 mm diameter flexible glass pH probe (Ingold). The probe was inserted through the nares, passed into the stomach to ensure that gastric acid was present, then positioned 87% of the distance from the tip of the nose to the gastro-oesophageal junction, the latter being determined according to the formula of Strobel *et al.*[11] In all cases position of the electrode was checked by fluoroscopy. The electrode was calibrated at the beginning and end of each study at pH 4·0 and 7·0 with buffer solutions. If the pH drift exceeded 0·3 pH unit, then the recording was discarded. A reference electrode was attached to the patient's chest. Oesophageal reflux was defined as a decrease in the pH to less than 4·0 for at least 15 seconds. Output from the pH probe was recorded on a modified Holter cassette recorder, which the patient carried on a belt (Proxima Light). All children were allowed to eat an unrestricted diet but snacks between meals were not allowed. The cassette recording was analysed by a computer program (Esophogram, Gastrosoft) on a IBM personal computer. The recording system had manual event markers. When pressed these markers enter an event specific code into the computer memory simultaneously with oesophageal pH.

The mother of each patient was instructed to press the event markers and record in a personal diary the following events: (a) beginning and end of the meals, (b) symptom occurrence, and (c) sleeping and awake periods. The following parameters were evaluated during each 24 hour oesophageal pH probe study: number of GOR episodes, percentage of time that intraoesophageal pH was less than 4·0 (percentage of GOR), number of long lasting GOR episodes (≥5 minutes), and mean duration of reflux episodes (minutes) (that is, the ratio between minutes of oesophageal acid exposure and number of GOR episodes). Measurement for each parameter was divided into awake and sleeping periods, and into intervals less than two hours (fed) and more than two hours after meals (fasting). In addition, intraoesophageal pH profile was inspected during periods of chest physiotherapy. Prolonged pH recordings obtained from patients with cystic fibrosis were compared with those from 10 age matched children who served as controls and are part of a larger study reported elsewhere.[12] These subjects were all referred to our unit by their physicians and underwent prolonged pH study because of symptoms suggesting GOR disease. Three of the controls had feeding problems caused by maternal anxiety, four had recurrent functional abdominal pain, and three had irritable bowel syndrome.

Combined recording of oesophageal motility and pH was performed for two hours, on a separate day, after a three hour fasting period. Oesophageal motility was monitored using a manometric assembly that incorporated a 4 cm sleeve sensor and four other catheters whose lumina terminated in side orifices located 1 cm distal to the distal sleeve margin, at the proximal sleeve margin, and 2·5 and 5 cm proximal to the sleeve. The sleeve sensor was positioned so that it straddled the lower oesophageal sphincter; intragastric pressure was recorded by the side hole located at the distal margin of the sleeve; the side holes located at the proximal sleeve margin and 2·5 cm proximal to the sleeve recorded oesophageal body pressure. The lower oesophageal sphincter was localised using the station pull through method. Pressures were transmitted to external transducers (Beckman 4-327-C) whose output was recorded on a rectilinear ink writing polygraph (Beckman R611).

The perfusion apparatus utilised during this investigation was a high fidelity pneumohydraulic capillary infusion pump (Arnodorfer Med Spec). The compliance of this system was low, having a pressure rise rate greater than 40 kPa (300 mm Hg)/second upon total occlusion at the individual catheter openings. A microphone attached to a DC coupler input was placed at the level of thyroid cartilage to detect swallows. A 1·6 mm diameter micro pH intraluminal electrode (Microelectrodes Inc) recorded intraoesophageal pH at a site corresponding to 87% of the distance nares to lower oesophageal sphincter. The electrode was connected to a Beckman pH meter (N39042) and the pH signals were recorded on the manometric polygraph. Function of the pH electrode was confirmed by checks with buffers of pH 4·0 and 7·0 at the start and end of each recording session. The manometric assembly and pH electrode were taped securely at the nose and the subjects were studied in a recumbent supine position.

Lower oesophageal sphincter basal pressure was measured every minute by subtracting the corresponding gastric fundal pressure. The sphincter pressure was not calculated during and immediately after relaxations of the sphincter and in correspondence with abdominal straining as indicated by increase of the fundic pressure. Transient relaxation of the lower oesophageal sphincter was defined as appropriate or inappropriate if it occurred with or without a complete peristaltic sequence in the oesophageal body, respectively. Relaxation of the lower oesophageal sphincter was defined as complete if the lower oesophageal sphincter pressure fell to within 0·53 kPa (4 mm Hg) or less of the end expiratory gastric pressure. After the occurrence of each episode of GOR we measured, in the distal oesophageal body, amplitude of primary peristalsis (defined as a peristaltic sequence preceded by a burst of activity from the neck microphone suggesting swallowing) and the incidence of non-specific oesophageal motor defects such as simultaneous, repetitive, or broad based waves. Amplitude of peristalsis was calculated as the pressure rise from baseline oesophageal pressure to peak pressure. Oesophageal primary peristalsis was defined as efficacious or inefficacious if it was able or not to raise intraluminal pH by at least 0·5 pH unit, respectively. The combined pH and manometric data from patients with cystic fibrosis were compared with those from other groups of patients in whom the pH-manometric study was performed in an identical fashion: 12 patients (mean age 3·5 years, range 6 months-10 years) with symptomatic GOR, eight patients with oesophagitis documented by endoscopy and biopsy (mean age 7·5 years, range 5–11 years), and seven patients with GOR disease complicated by recurrent respiratory symptoms such as asthma or pneumonia (mean age 4 years, range 6 months-12 years). In the latter patients respiratory symptoms were considered reflux related because they improved with adequate antireflux regimen.

Patients with cystic fibrosis and pathological GOR were treated for eight weeks with cisapride, a new non-dopamine receptor blocking prokinetic drug, and postural treatment consisting of a prone position raised by 30°. Cisapride was given orally before meals in a dose of 0·6 mg/kg/day in three equally divided doses, eight hours apart. Three days after the end of the therapeutic trial patients underwent 24 hour intraoesophageal pH monitoring.

The study was approved by the ethical committee of our faculty and informed written consent was obtained from the parents. All data were expressed as mean (SD); the unpaired Student's *t* test, Wilcoxon's signed rank test, and the χ^2 test were used for statistical evaluation of data.

Results

The results of analysis of continuous intraoesophageal pH monitoring are shown in

Table 1 Analysis of continuous oesophageal pH recordings in patients with cystic fibrosis and controls. Values given as mean (SD)

	Cystic fibrosis	*Controls*
Overall record:		
Time <pH 4·0 (%)	11·20 (0·30)	1·85 (0·82)*
Episodes lasting ≥5 min	8·14 (4·60)	0·90 (1·04)*
Mean duration (min)	5·01 (2·35)	3·01 (0·23)**
No of episodes	38·20 (20·10)	12·90 (8·66)*
Fed period:		
Time <pH 4·0 (%)	4·57 (3·67)	0·48 (0·50)*
Episodes lasting ≥5 min	3·64 (4·04)	0·10 (0·30)*
Mean duration (min)	3·96 (2·85)	1·42 (1·73)†
No of episodes	18·70 (14·30)	5·60 (7·48)**
Fasting period:		
Time <pH 4·0 (%)	6·60 (3·78)	1·80 (0·89)*
Episodes lasting ≥5 min	4·57 (2·76)	0·80 (0·97)**
Mean duration (min)	5·35 (3·16)	2·86 (2·47)†
No of episodes	19·70 (10·40)	7·30 (5·13)*
Awake period:		
Time <pH 4·0 (%)	5·80 (4·30)	1·06 (0·78)*
Episodes lasting ≥5 min	4·64 (4·55)	0·10 (0·30)*
Mean duration (min)	3·71 (1·81)	2·33 (1·33)†
No of episodes	30·80 (18·80)	10·30 (8·59)*
Sleeping period:		
Time <pH 4·0 (%)	5·06 (4·86)	0·78 (0·65)**
Episodes lasting ≥5 min	3·50 (3·43)	0·80 (1·07)**
Mean duration (min)	6·80 (4·50)	3·52 (2·40)**
No of episodes	8·85 (6·40)	2·90 (1·70)*

*p<0·01, **p<0·05, †NS.

table 1. In 12 patients with cystic fibrosis the per cent of time that distal oesophageal pH was less than 4·0 was 2SD greater than that in controls. As indicated in the table, an abnormal GOR was homogeneously distributed among the various phases of the temporal analysis of the pH tracings. During periods of chest physiotherapy intraoesophageal pH profile did not show an increased rate of reflux. The 12 patients with cystic fibrosis who had evidence of pathological GOR from measurement of pH underwent simultaneous oesophageal manometric and pH study. Basal lower oesophageal sphincter pressure in patients with cystic fibrosis, 2·9 (0·9) kPa (21·8 (6·5) mm Hg), did not significantly differ from that detected in patients with symptomatic GOR, 3·2 (0·7) kPa (23·6 (4·9) mm Hg), and in patients with oesophagitis, 2·5 (0·5) kPa (18·7 (4·1) mm Hg). Patients with GOR disease complicated by respiratory symptoms had a basal lower oesophageal sphincter pressure of 1·3 (0·2) kPa (9·7 (1·3) mm Hg) that was significantly lower than that recorded in the other groups (p<0·05). Intrathoracic to intra-abdominal pressure gradient was not significantly different in the various groups of patients: cystic fibrosis, 1·0 (0·3) kPa (7·6 (2·1) mm Hg); GOR alone, 1·2 (0·3) kPa (8·7 (1·9 mm Hg); oesophagitis, 1·1 (0·1) kPa (8·0 (0·9) mm Hg); and GOR and respiratory disease, 1·1 (0·1) kPa (8·3 (0·7) mm Hg). Patients with cystic fibrosis had a total of 75 episodes of acid reflux, whereas 86, 84, and 63 episodes of acid reflux were detected in patients with symptomatic GOR, oesophagitis, and GOR disease complicated by respiratory symptoms, respectively. The majority of episodes of acid GOR in cystic fibrosis patients (53·3%), in patients with symptomatic GOR (25·6%), and in patients with reflux oesophagitis (51·2%) were associated with an identifiable inappropriate transient lower oesophageal sphincter relaxation (fig 1). In patients with GOR disease and respiratory symptoms, gradual decrease of lower oesophageal sphincter pressure to very low values (lower oesophageal sphincter pressure drift) was the most prevalent mechanism accounting for 38·1% of reflux episodes. The proportion of reflux episodes associated with the different types of reflux mechanism in the study groups is reported in table 2. Episodes of inappropriate lower oesophageal sphincter relaxation associated with reflux were evenly distributed in all patients with cystic fibrosis.

Analysis of motor events of the oesophageal body during acid exposure showed that amplitude of primary peristalsis in patients with cystic fibrosis was 7·1 (2·9) kPa (53·2 (21·5) mm Hg) and significantly lower than in patients with symptomatic GOR, 9·3 (2·6) kPa (70·1 (19·2) mm Hg) (p<0·05), but did not differ from that measured in patients with oesophagitis, 6·4 (1·9) kPa (47·8 (14·1) mm Hg) and in patients with GOR disease and respiratory symptoms, 8·1 (0·7) kPa (60·7 (5·1) mm Hg). The ability of primary peristalsis to clear acid from the lumen of the oesophagus (percentage of waves capable to raise intraluminal pH by at least 0·5 pH units) in cystic fibrosis patients (53·2%) was lower than in patients with symptomatic GOR (70·1%, χ^2 7·5, p<0·01), but did

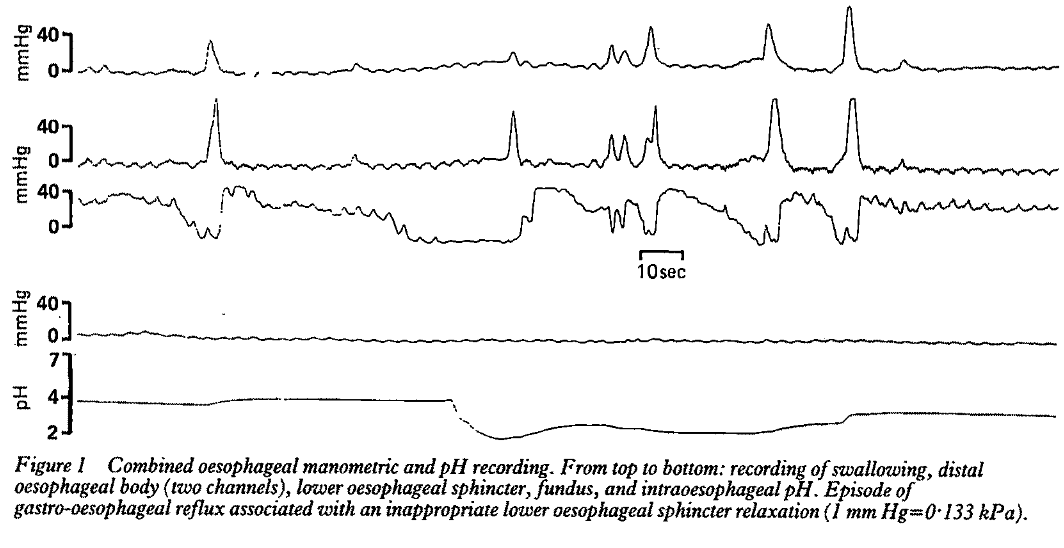


Figure 1 Combined oesophageal manometric and pH recording. From top to bottom: recording of swallowing, distal oesophageal body (two channels), lower oesophageal sphincter, fundus, and intraoesophageal pH. Episode of gastro-oesophageal reflux associated with an inappropriate lower oesophageal sphincter relaxation (1 mm Hg=0·133 kPa).

Table 2 Percentage of reflux episodes associated with various pathogenetic mechanisms in the study groups

	Cystic fibrosis (n=14)	*GOR alone (n=12)*	*Reflux oesophagitis (n=8)*	*GOR with respiratory complications (n=7)*
Inappropriate LOS relaxations*	53·3	25·6	51·2	36·5
Appropriate LOS relaxations	14·9	24·4	26·2	19·0
Increased gastric pressure§	8	19·7	3·6	1·6
Low LOS pressure†	6·6	16·3	13·1	38·1
Combined mechanisms‡	17·3	13·9	6·0	4·76

Cystic fibrosis *v* GOR alone: $^*\chi^2$ 11·8, p<0·01.
Cystic fibrosis *v* GOR and respiratory disease: $\dagger\chi^2$ 18, p<0·01; $\ddagger\chi^2$ 4·1, p<0·05.
GOR alone *v* oesophagitis: $\S\chi^2$ 5·49, p<0·01.
GOR alone *v* GOR and respiratory disease: $\dagger\chi^2$ 7·9, p<0·01; $\S\chi^2$ 9·6, p<0·01.
Oesophagitis *v* GOR and respiratory disease: $\dagger\chi^2$ 5·2, p<0·05.
LOS, lower oesophageal sphincter.

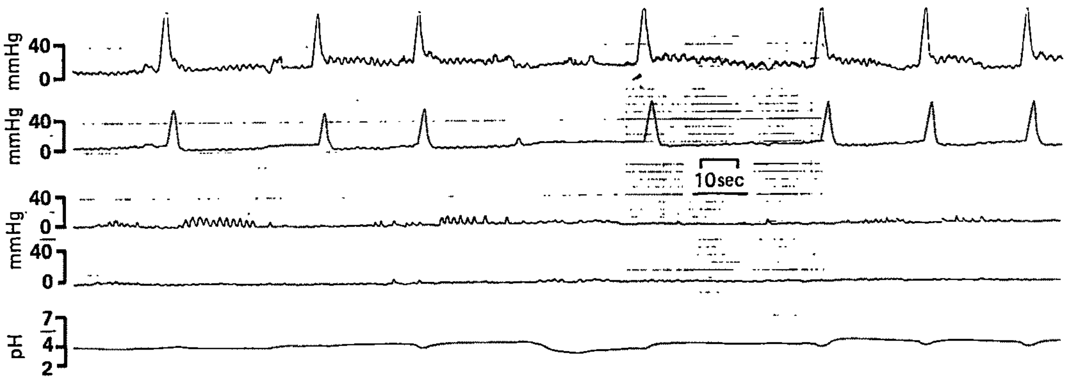


Figure 2 Combined oesophageal manometric and pH recording. From top to bottom: recording of swallowing, distal oesophageal body (two channels), lower oesophageal sphincter, fundus, and intraoesophageal pH. Episode of gastro-oesophageal reflux associated with lower oesophageal sphincter decrease (1 mm Hg=0·133 kPa).

Table 3 Prolonged intraoesophageal pH variables (% of GOR and episodes lasting ≥5 minutes) in seven children affected by cystic fibrosis and pathologic GOR treated with cisapride and postural treatment

Case Nos	*24 Hours*		*Asleep*		*Awake*		*Fed*		*Fasting*	
	% GOR	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*
					Baseline					
1	18·5	14	10·2	7	8·3	7	8·9	6	9·5	7
2	9·6	6	0·2	0	9·3	6	4·1	3	5·4	3
3	15·5	4	11·9	3	3·6	1	6·7	2	8·8	3
4	7·6	6	7·2	5	0·4	1	1·9	2	5·6	4
5	7·3	6	0·9	1	6·3	5	2·1	1	5·1	5
6	6·1	5	0·2	0	5·9	5	2·7	2	3·3	3
7	10·0	6	2·0	2	7·9	4	5·6	3	4·3	3
Mean	10·6	6·7	4·6	2·5	5·9	4·1	4·5	2·7	6·0	4
SD	4·3	3·0	4·6	2·4	2·8	2·1	2·4	1·5	2·1	1·4
					After the trial					
1	16·7	18	7·0	4	9·7	14	6·7	10	10·0	8
2	1·1	0	0	0	1·1	0	0·05	0	1·1	0
3	13·5	10	0	0	13·0	10	7·1	6	5·9	4
4	3·2	2	0·8	2	2·3	0	0·7	0	2·5	2
5	12·9	7	7·1	5	5·7	2	4·0	1	8·8	6
6	0·04	0	0·04	0	0	0	0	0	0·04	0
7.	11·9	7	1·8	1	10·1	6	8·3	6	3·5	1
Mean	8·47	6·3	2·39	1·7	5·9	4·5	3·8	3·3	4·5	3
SD	6·3	5·9	3·0	1·9	4·6	5·2	3·3	3·7	3·5	2·8

not differ from that detected in oesophagitis patients (42·3%) and in GOR patients with respiratory complaints (53·6%). The incidence of non-specific motor defects during endogenous acid exposure in patients with cystic fibrosis (17·5%) was significantly higher than in symptomatic GOR patients (8·6%; χ^2 5·1, p<0·05), but did not statistically differ from that recorded in the other study groups (oesophagitis 13·8%, GOR and respiratory disease 9·25%).

Only seven patients with cystic fibrosis completed the eight week therapeutic course with cisapride and posture. Table 3 shows the before and after treatment values of both GOR percentage (oesophageal acid exposure time) and GOR episodes lasting more than five minutes for each patient, in the various phases of pH analysis. The oesophageal acid exposure time and the number of reflux episodes lasting more than five minutes became normal in only three patients and were unaffected in the other four patients.

Discussion

It is generally recognised that primary pulmonary disorders such as cystic fibrosis, bronchopulmonary dysplasia, or respiratory infections can provoke GOR.[1] Both symptomatic and objectively documented reflux has been described in patients with cystic fibrosis. Scott *et al*[8] and Forster *et al*[7] detected by intraoesophageal pH measurement abnormal oesophageal acid exposure in a subgroup of cystic fibrosis patients complaining of symptoms of GOR; others have reported the presence of oesophageal injury from acid reflux in children with cystic fibrosis.[6 9]

The reason for an increased incidence of GOR in a wide variety of primary respiratory disorders is unknown. The most commonly considered mechanism is an increase of transdiaphragmatic pressure by the forced expiration of coughing and wheezing.[1] It is also potentially possible that periodic coughing provokes GOR by intermittently raising abdominal pressure. Recent studies have revealed that active diaphragmatic contraction during spontaneous breathing is responsible for respiratory induced pressure oscillations of the lower oesophageal sphincter that are commonly observed during manometric evaluation of the sphincter.[13] Furthermore, there is experimental evidence that contraction of crural diaphragm increases the barrier to movement across the gastro-oesophageal sphincter.[14] Therefore it is tempting to suggest that abnormalities in diaphragmatic performance might predispose the patient with primary respiratory disorders to the development of GOR. Our patients with cystic fibrosis and pathological GOR did not exhibit a decreased basal lower oesophageal sphincter pressure; furthermore, no disturbance in thoracoabdominal pressure gradient was detected in them. The predominant reflux mechanism in our cystic fibrosis patients was transient lower oesophageal sphincter relaxation, without a peristaltic sequence in the oesophageal body. Inappropriate transient lower oesophageal sphincter relaxations were also found to account for the majority of episodes of GOR in patients with symptomatic GOR and in patients with oesophagitis, whereas in patients with GOR related respiratory disease episodes of gradual decrease of basal lower oesophageal sphincter pressure were as common as transient lower oesophageal sphincter relaxation events. An excessively frequent rate of occurrence of spontaneous transient lower oesophageal sphincter relaxations is currently believed to be the most important abnormality that underlies pathological GOR. Gradual decrease of basal lower oesophageal sphincter tone has been shown to lead to reflux in a minority of patients.[15]

Triggers for transient lower oesophageal sphincter relaxation are not fully understood. Recently it has been suggested that transient inappropriate lower oesophageal sphincter relaxations are mediated by a neural mechanism involving active neural inhibition either by pharyngeal stimuli subthreshold for triggering a swallow or by sensory stimuli from the stomach.[16] The high frequency of transient inappropriate relaxations of the lower oesophageal sphincter in our cystic fibrosis patients with pathologic GOR is consistent with experimental observations of Boyle *et al*—who have demonstrated that lung inflation provokes transient lower oesophageal sphincter relaxation by a reflex mechanism involving sensory input from vagal afferent fibres in the lung.[17 18]

Patients with pulmonary symptoms secondary to GOR showed a decreased basal lower oesophageal sphincter pressure compared with the other groups. However, their lower oesophageal sphincter pressure value is commonly considered to be sufficient to prevent GOR, also during episodes of increased intra-abdominal pressure.[19] Most reflux episodes in GOR related respiratory patients occurred during intermittent episodes of lower oesophageal sphincter pressure drift. Nevertheless, reflux episodes due to inappropriate lower oesophageal sphincter relaxations were also common in this population and their incidence did not statistically differ from that detected in cystic fibrosis patients. Both inappropriate lower oesophageal sphincter relaxation and lower oesophageal sphincter pressure drift are currently considered as intermittent episodes of deranged neural control of lower oesophageal sphincter pressure.[15]

During oesophageal manometry patients with GOR related respiratory complaints had both a normal pulmonary function and a normal chest *x* ray picture; furthermore, none of them received bronchodilator treatment. These observations suggest that manometric patterns in these patients do not seem to be secondary to pulmonary disease.

Only seven patients with cystic fibrosis underwent a complete therapeutic course consisting of administration of a prokinetic drug, cisapride, and postural treatment. The prolonged intraoesophageal pH monitoring at the end of the trial showed that oesophageal acid exposure was not improved in the majority of patients. Indeed, if one assumes that in primary respiratory disorders, transient lower oesophageal sphincter inhibition can be induced by stimulation of pulmonary afferents,[18] we suggest that unremitting chronic respiratory disorders might be a source of persisting lower oesophageal sphincter inhibition by a reflex mechanism. On the other hand, failure of cisapride to decrease oesophageal acid exposure in the majority of patients with cystic fibrosis who completed the therapeutic trial, can be explained by the lack of effects on the rate of transient lower oesophageal sphincter relaxation by the prokinetic drugs.[20]

The present study has confirmed that pathological GOR is common in cystic fibrosis patients. It appears to be a serious event because of the presence of both manometric abnormalities of the oesophageal body and significant degrees of nocturnal reflux; furthermore, medical treatment can be unsatisfactory. GOR should be properly investigated in children with cystic fibrosis through a complete medical interview and appropriate diagnostic tests such as prolonged intraoesophageal pH monitoring.

1 Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. *J Pediatr* 1988;112:847–58.
2 Barish CF, Wu WC, Castell DO. Respiratory complications of gastroesophageal reflux. *Arch Intern Med* 1985;145: 1882–8.
3 Nelson HS. Gastroesophageal reflux and pulmonary disease. *Allergy Clin Immunol* 1984;73:547–56.
4 Allen CJ, Newhouse MT. Gastroesophageal reflux and chronic respiratory disease. *Am Rev Respir Dis* 1984;129: 645–57.

5 Boyle JT. Gastroesophageal reflux in the pediatric patient. *Gastroenterology Clinics of North America* 1989;**18**:315–7.

6 Bendig DW, Wagner ML, Harrison GM. Complications of gastroesophageal reflux in patients with cystic fibrosis. *J Pediatr* 1982;**100**:536–40.

7 Forster AC, Voyles JB, Murphy SA. Twenty four hour pH monitoring in children with cystic fibrosis: association of chest physical therapy to gastroesophageal reflux. *Pediatr Res* 1983;**17**:188.

8 Scott RB, O'Loughlin EV, Gall DG. Gastroesophageal reflux in patients with cystic fibrosis. *J Pediatr* 1985;**106**:223–7.

9 Vinecour CD, Marmon L, Schidlow DV, Weintraub WH. Gastroesophageal reflux in the infant with cystic fibrosis. *Am J Surg* 1985;**149**:182–6.

10 Chrispin AR, Norman AP. The systematic evaluation of the chest radiograph in cystic fibrosis. *Pediatr Radiol* 1974;**2**: 101–6.

11 Strobel CT, Byrne WJ, Ament Me, Euler AR. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. *J Pediatr* 1979;**94**:81–4.

12 Cucchiara S, Staiano A, Gobio Casali L, Boccieri A, Paone FM. Value of the 24 hour intraoesophageal pH monitoring in children. *Gut* 1990;**31**:129–33.

13 Boyle JT, Altschuler SM, Nixon TE, Tuchman DN, Pack AL, Cohen S. Role of the diaphragm in the genesis of the lower esophageal sphincter pressure in the cat. *Gastroenterology* 1985;**88**:723–30.

14 Williams TA, Altschuler SM, Hanna YJ, Boyle JT. Diaphragmatic contraction enhances the barrier to movement across the gastroesophageal junction during spontaneous respiration. *Gastroenterology* 1987;**92**:1696.

15 Dent J, Holloway RH, Touli J, Dodds WJ. Mechanism of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. *Gut* 1988;**29**: 1020–8.

16 Mittal RK, McCallum RW. Characteristics and frequency of transient relaxation of the lower esophageal sphincter in patients with reflux esophagitis. *Gastroenterology* 1988;**95**: 593–9.

17 Boyle JT, Altschuler SM, Patterson BL, Pack AL, Cohen S. Reflex inhibition of the lower esophageal sphincter (LES) following stimulation of pulmonary vagal afferent receptors. *Gastroenterology* 1986;**90**:1353.

18 Boyle JT, Patterson BL, Hanna Y. Reflex inhibition of the lower esophageal sphincter (LES) following stimulation of bronchopulmonary non-myelinated c-fibers. *Gastroenterology* 1988;**94**:46.

19 Dent J, Dodds WJ, Hogan WJ, Toouli J. Factors that influence induction of gastroesophageal reflux in normal human subjects. *Dig Dis Sci* 1988;**33**:270–5.

20 Reynolds JC. Prokinetic agents: a key in the future of gastroenterology. *Gastroenterology Clinics of North America* 1989; **18**:437–57.

Towards a universal vaccine for atopy?

The possibility of a different and more fundamental kind of immunotherapy is raised by workers in Birmingham (Stanworth *et al*, *Lancet* 1990;**336**:1279–81). A 10 amino acid peptide, which is part of the human IgE molecule, was synthesised and conjugated with protein. The peptide-protein conjugate was then used to immunise rabbits. The serum from these rabbits inhibited mast cell activation in rats. The authors showed firstly that the rabbit antiserum reduced the histamine release induced by incubating the rat mast cells with human ε chain decapeptide solution. Secondly, they demonstrated that an intravenous injection of the antiserum inhibited the cutaneous reaction produced when rats given an intradermal injection of serum from rats sensitised to ovalbumin were injected intravenously with ovalbumin.

Immunisation of rats with the peptide-protein conjugate either before or after sensitising them to ovalbumin much reduced the serum histamine response to ovalbumin challenge and those immunised before sensitisation were protected from anaphylaxis induced by intravenous ovalbumin. A vaccine made from a rat peptide-protein conjugate had similar protective effects, being immunogenic possibly because the peptide is hidden within the IgE molecule and therefore not recognised as self. This gives hope that it might be possible to immunise people with the human peptide.

The authors suggest that clinical trials should now be carried out. There seems a long way to go before this work can be shown to apply to atopic patients but the potential is obvious and exciting. Future developments will be followed with very great interest.

ARCHIVIST

Archives of Disease in Childhood 1991; **66:** 623–626

Computed tomography of the brain in kwashiorkor: a follow up study

K C Househam

Abstract

Computed tomography of the brain was performed initially and after nutritional rehabilitation on 12 children with kwashiorkor. The severe cerebral shrinkage evident initially resolved after nutritional rehabilitation. The mechanism and significance of this reversible abnormality remains to be determined.

The effect of severe protein energy malnutrition on the developing brain remains a controversial issue. In a previous report the presence of cerebral atrophy or brain shrinkage in eight children with kwashiorkor was described.[1] The precise nature of the loss of brain volume was uncertain. To determine the implications of these findings a follow up study was undertaken.

Patients and methods

Twelve children aged 11 to 28 months (median 17·7 months) were studied. Seven were girls and all were admitted primarily for management of severe protein energy malnutrition. One child had significant gastroenteritis that required rehydration and correction of a metabolic acidosis.

On inclusion into the study the children were assessed clinically and by means of computed tomography of the brain. All subjects were normally hydrated and clinically stable at the time of the computed tomography. The scans were carried out two to three weeks after admission. The tomograms of the brain were performed according to standard procedures without contrast.

Consent was obtained from the parents in each case. The study was approved by the ethical committee of the Medical Faculty of the University of the Orange Free State.

The children were discharged for further nutritional rehabilitation at home. They were followed up and re-evaluated on average 14 months after the initial assessment.

Results

Initially all but one of the children were significantly growth retarded (table) with masses less than 80% of the expected 50th National Center for Health Statistics centiles.[2] Mean expected weight for age was 68·9%. In two the masses were less than 60% of expected weights for age, indicating severe malnutrition or marasmic kwashiorkor. The mean expected height for age was 92·2%. Head circumference was measured initially in 11 and was normal in seven children. In all patients the head circumference appeared appropriate to the body size.

Nutritional and growth variables in 12 cases before and after nutritional rehabilitation

Case No	*Mass (% EW)**		*Head circumference (NCHS centile)†*		*Albumin (g/l)*	
	Before	*After*	*Before*	*After*	*Before*	*After*
1	79	90	<3	<3	16	36
2	63	84	50	48	16	43
3	71	81	75	60	13	37
4	63	86	<3	25	16	46
5	71	102	25	75	14	43
6	72	81	<3	25	19	34
7	54	83	Missing	50	23	43
8	80	90	60	96	24	36
9	50	85	<3	38	22	Missing
10	60	92	30	40	14	41
11	87	106	90	97	15	42
12	76	95	25	50	20	38

*% EW=percentage of expected weight for age.
†NCHS=National Center for Health Statistics.[2]

Serum albumin concentrations were low in all patients (mean 17·7 g/l) and in eight were below 20 g/l. All had clinical features typical of kwashiorkor such as generalised oedema, skin lesions, and hair changes. All were typically apathetic and withdrawn on admission.

The computed tomograms showed cerebral atrophy in all 12 children. In eight there appeared to be a severe degree of atrophy with pronounced enlargement of the ventricles and cerebral sulci. There were no other abnormalities evident on computed tomography.

At restudy after a mean of 14 months (range 9·3 to 24·1 months) the children all were nourished normally with masses and heights greater than 80% of the expected for age (table). The head circumference was normal in 11 children. In the remaining child the head circumference was just below the third centile when it previously had been far below this centile. The child had no signs of gross neurological deficit. The serum albumin concentrations were normal in 11 children with one value of 34 g/l just below normal (mean 39·9, range 34–46 g/l).

The computed tomograms in all children showed dramatic improvement with 11 of the 12 being within the limits of normal. Tomograms before and after nutritional rehabilitation are shown in fig 1 and 2. In one child the cerebral atrophy had resolved but there was a residual abnormality of the left parietal cortex with widening of the sulci and a loss of cerebral cortex. This was suggestive of an old cerebral infarction (fig 3). The patient had no neurological signs on physical examination.

Discussion

The results of this study demonstrate the dra-

Department of Paediatrics and Child Health, Faculty of Medicine, University of the Orange Free State, PO Box 339 (G69) Bloemfontein 9300, Republic of South Africa

Correspondence to:
Professor Househam.

Accepted 5 November 1990

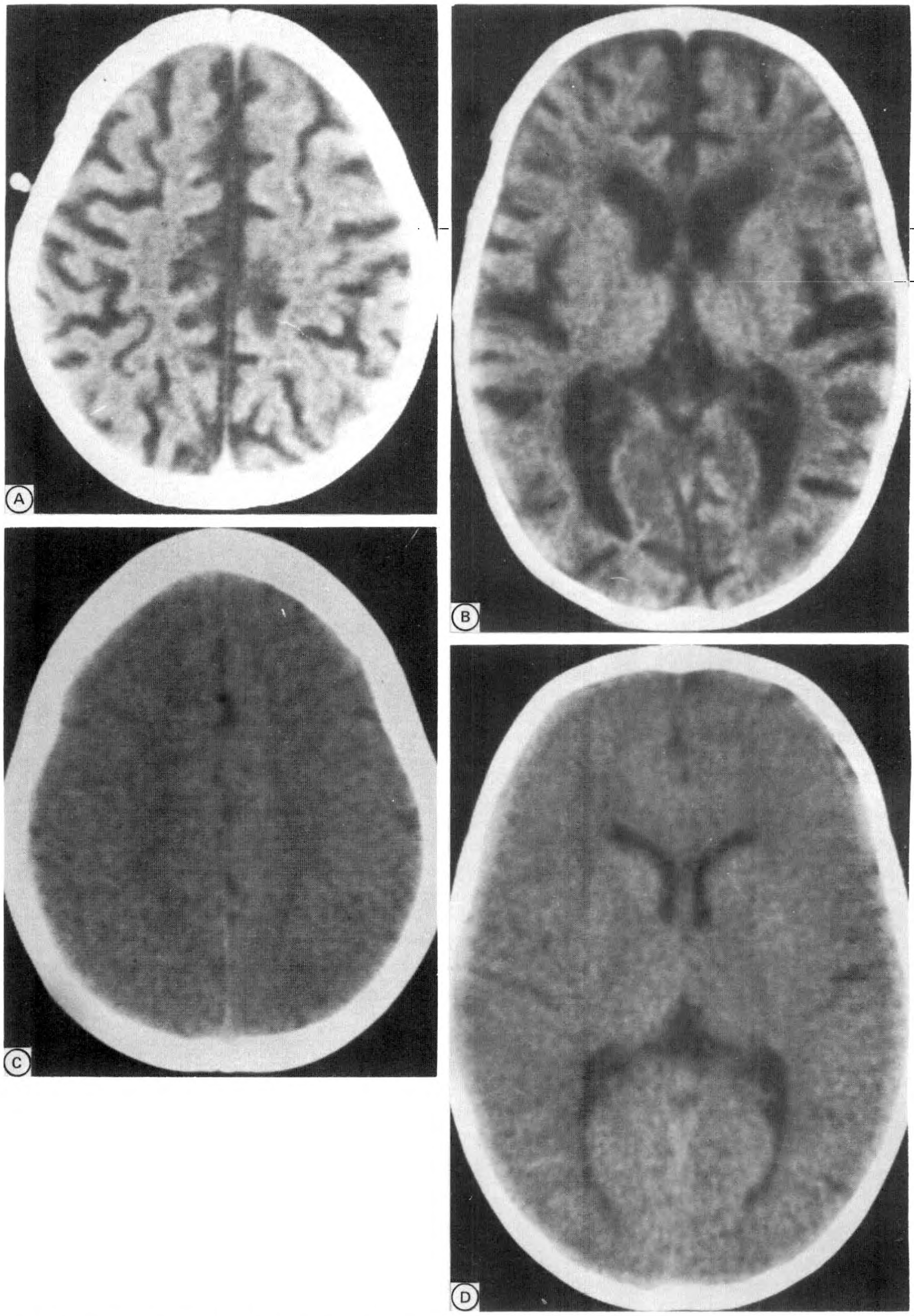


Figure 1 Computed tomograms of case 8 (A) and (B) showing widened cerebral sulci and enlarged ventricles and (C) and (D) after nutritional rehabilitation for one year showing a normal appearance.

matic resolution of the cerebral shrinkage found in all patients during the acute phase of kwashiorkor, an average of 14 months after the commencement of nutritional rehabilitation. During this time the nutritional state of the children also had improved and they appeared well generally with no sequelae of the preceding episode of severe kwashiorkor.

No definite neuropathology has been associated previously with protein energy malnutrition. In animal studies cell migration and the elaboration of cell processes in the brain are affected negatively.[3] The cell morphology remains normal but cell numbers in the brain may be decreased.[4] The glial cells mainly are affected with reduction in the lipid content of the myelin membrane.[5 6]

Work in animals and observations in humans indicate that severe protein energy malnutrition at a time of rapid brain growth in infancy and early childhood is associated with reduced head size and brain weight.[7–9] Work done during the

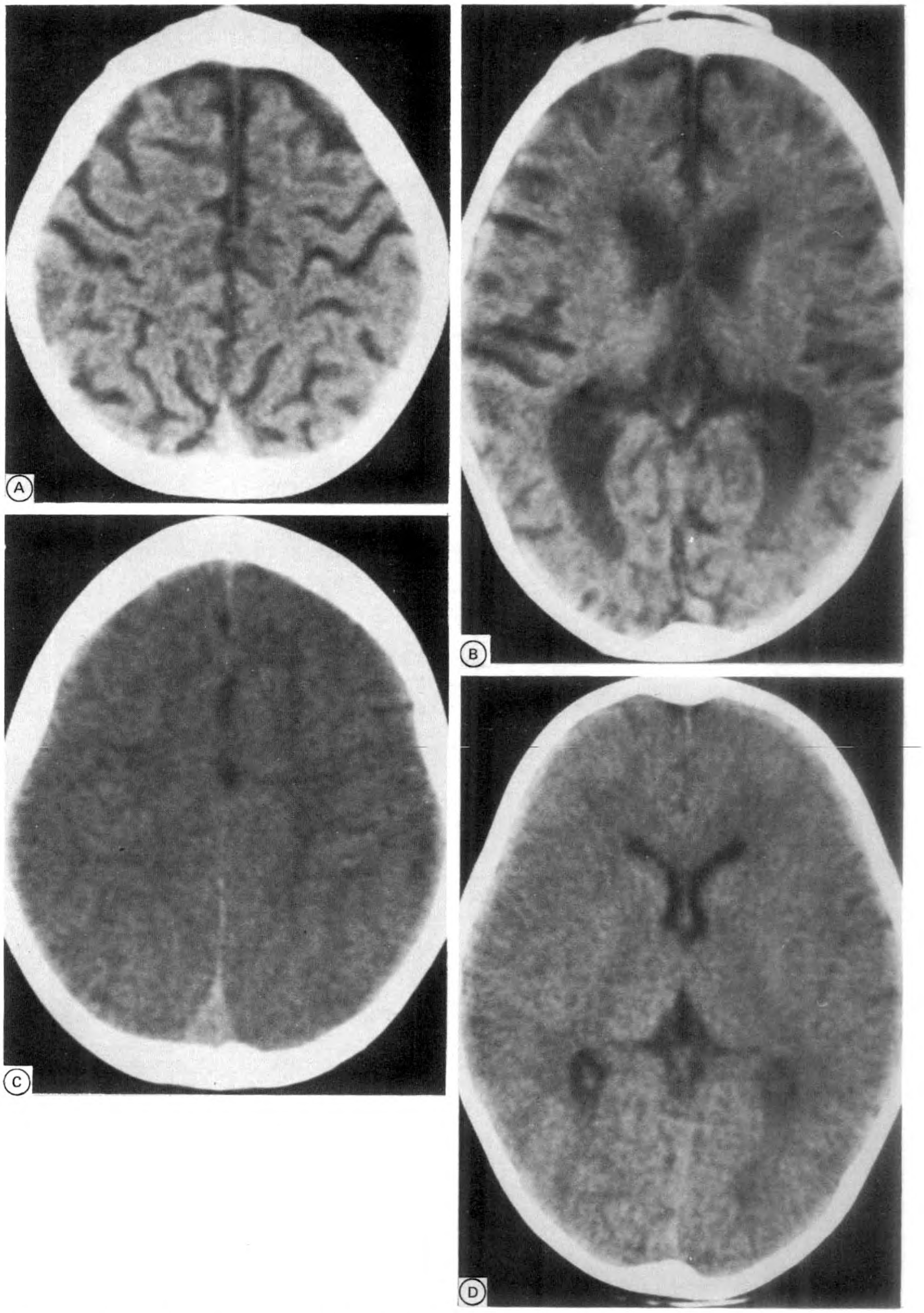


Figure 2 Computed tomograms of case 11 (A) and (B) showing diffuse cerebral shrinkage and (C) and (D) after nutritional rehabilitation for 14·8 months showing a normal appearance.

early 1970s demonstrated increased transillumination over the cerebrum suggesting shrinkage of the intracranial contents in infants with severe marasmus and kwashiorkor.[10 11] The cerebrospinal fluid in these children was normal and there was free circulation of the cerebrospinal fluid excluding the possibility of subdural effusions.[10] It was assumed that the increase in cerebrospinal fluid was relative due to loss of brain substance or cerebral atrophy. Echoencephalographic studies of Ethiopian children with kwashiorkor produced similar findings.[12] These studies are in conformity with the cerebral shrinkage or atrophy demonstrated on computed tomography in our studies. The important question concerns the nature of the cerebral shrinkage and whether the changes are reversible.

In a further study of Ethiopian children over the age of 2 years of age with marasmic

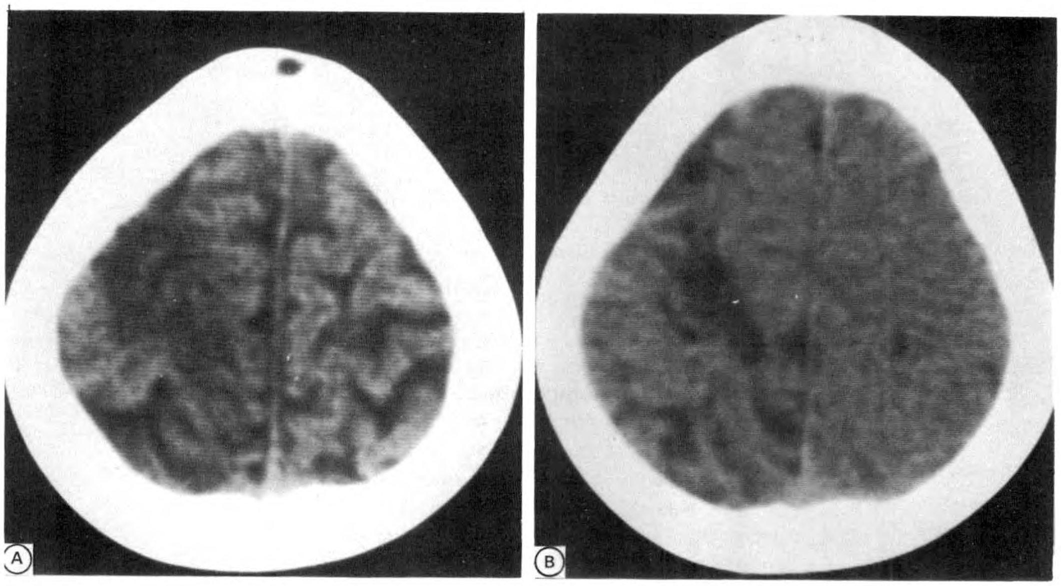


Figure 3 Computed tomogram of case 2 (A) showing cerebral shrinkage and a left cortical abnormality and (B) after nutritional rehabilitation for 10·6 months with a persisting left cortical abnormality.

kwashiorkor the increased transillumination demonstrated disappeared after nutritional treatment.[11] This finding corresponds with that of the present study in that the cerebral shrinkage demonstrated on computed tomography resolved with nutritional rehabilitation.

As there is no detectable neurological deficit in these children, apart from apathy and irritability, significant neuronal loss is unlikely. Loss of interstitial fluid is a further possible cause of cerebral shrinkage. As interstitial fluid generally is increased due to a decreased serum oncotic pressure in kwashiorkor, however, this pathogenesis would seem unlikely. It must be stressed that the investigations by computed tomography were performed in patients who were hydrated normally and showed no electrolyte imbalance.

In view of the fact that the lipid content of the brain has been shown to decrease in severe protein energy malnutrition[5 6] it may be postulated that loss of myelin lipid accounts for the cerebral shrinkage seen in the acute phase of this condition. In an animal study Benton *et al* demonstrated a restoration of brain lipids after nutritional rehabilitation.[5] It is possible that restoration of lipid to the myelin membrane may account for reversal of the cerebral shrinkage.

In conclusion, it is apparent that further studies of the brain in protein energy malnutrition are required. Postmortem studies in children dying of acute protein energy malnutrition, and in vivo studies by means of nuclear magnetic resonance, may provide the answer.

1 Househam KC, de Villiers JFK. Computed tomography in severe protein energy malnutrition. *Arch Dis Child* 1987;**62**:589–92.
2 Hamil PVV, Dridzl TA, Johnson CL, *et al*. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979;**32**:607–29.
3 Dobbing J, Hopewell JW, Lynch A. Vulnerability of developing brain. VII. Permanent deficit of neurons in cerebral and cerebellar cortex following early mild undernutrition. *Exp Neurol* 1971;**32**:439–47.
4 Winick M, Rosso P, Waterlow J. Cellular growth of cerebrum, cerebellum and brainstem in normal and marasmic children. *Exp Neurol* 1970;**26**:393–400.
5 Benton JW, Moser HW, Dodge PR, Carr S. Modification of the schedule of myelination in the rat by early nutritional deprivation. *Pediatrics* 1966;**38**:801–7.
6 Bass NH, Netsky MG, Young E. Microchemical studies of postnatal development of rat cerebrum. II Formation of myelin. *Neurology* 1969;**19**:405–14.
7 Stoch MB, Smythe PM. The effect of undernutrition during infancy on subsequent brain growth and intellectual development. *S Afr Med J* 1967;**41**:1027–30.
8 Pretorius PJ, Novis H. Nutritional marasmus in Bantu infants in the Pretoria area. II. Clinical and pathological aspects. *S Afr Med J* 1965;**39**:501–5.
9 Graham G, Morales E. Studies in infantile malnutrition. I. Nature of the problem in Peru. *J Nutr* 1963;**79**:479–87.
10 Rozovoski JN, Novoa FS, Arbarzua JF, Monckeberg FB. Cranial transillumination in early and severe malnutrition. *Br J Nutr* 1971;**25**:107–11.
11 Engsner G, Belete S, Sjogren I, Vahlquist B. Brain growth in children with marasmus. A study using head circumference measurement, transillumination and ultrasonic echo ventriculography. *Ups J Med Sci* 1974;**79**:116–28.
12 Vahlquist B, Engsner G, Sjogren I. Malnutrition and size of the cerebral ventricles. Echoencephalographic studies in infants and young children: preliminary communication. *Acta Paediatr Scand* 1971;**60**:533–9.

Archives of Disease in Childhood 1991; **66:** 627–632

How mothers keep their babies warm

C J Bacon, S A Bell, E E Clulow, A B Beattie

Abstract

Details of room temperature, clothing, and bedding used by night and by day and in winter and in summer were recorded for 649 babies aged 8 to 26 weeks. Room temperature at night was significantly related to outside temperature and duration of heating. Total insulation was significantly related to outside temperature and to minimum room temperature, but there was wide variation in insulation at the same room temperature. High levels of insulation for a given room temperature were found particularly at night and in winter, and were associated with the use of thick or doubled duvets and with swaddling. At least half the babies threw off some or all of their bedding at night, and at least a quarter sweated. Younger mothers and mothers in the lower social groups put more bedclothes over their babies, and the latter also kept their rooms warmer. Many mothers kept their babies warmer during infections.

There has recently been interest in the thermal environment of sleeping babies, arising mainly from suggestions that some cases of sudden infant death syndrome (SIDS)[1–4] and haemorrhagic shock and encephalopathy syndrome (HSES)[5] may be linked with overheating. A difficulty in evaluating this hypothesis has been the lack of control data. There have been four published surveys, from Exeter,[6] Nottingham,[7] Leicester,[8] and Dunedin (New Zealand),[9] of how mothers keep their babies warm.

We present the findings of a population survey of the thermal environment of 649 sleeping babies by day and night in summer and in winter.

Table 1 Class distribution of study group according to father's occupation compared with the OPCS 10% sample (1986)[10]

	No (%) of study group (n=649)	*OPCS 10% sample*
I	69 (10·6)	7·5
II	115 (17·7)	14·2
III Non-manual	94 (14·5)	11·3
III Manual	214 (33·0)	32·4
IV	69 (10·6)	14·3
V	76 (11·7)	10·8
Unclassified	12 (1·8)	9·5

Subjects and methods

A total of 978 mothers living in the Newcastle health district were randomly selected by systematic sampling from birth notifications over a period of three years (1985–7) and were approached for interview. Of these 329 (33·6%) declined to participate or were not available. The social class distribution (by father's occupation) of the 649 mothers who accepted was skewed towards the upper end of the scale compared with the 10% sample of births for Newcastle reported for 1986 by the Office of Population Censuses and Surveys (OPCS) (table 1).[10] There were few families from ethnic minorities. One person using a standard questionnaire interviewed these 649 mothers, once only, when their babies were about 8 weeks (n=204), 16 weeks (n=238), or 26 weeks old (n=207). The interviewer recorded full details of clothing and bedding used for the baby's sleep the previous night and for sleep on the day of the visit, inspecting all items to check their type and material. She also recorded the social background of the family, the gestation and birth weight of the baby, the type and duration of heating, the ventilation of the room, whether the baby sweated while sleeping, and what adjustments the mother made if the baby had an infection.

The ambient temperature of the baby's sleeping place was measured, for day by a recording at the time of the visit, for night by a maximum-minimum thermometer left near the cot and collected next morning (temperature recordings were not available for three babies). Outside temperatures for the same times were obtained from the Meteorological Office. The study continued through all months of the year except August. The data were analysed separately for the 326 mothers who were interviewed in summer and the 323 who were interviewed in winter, summer being defined as the period of British summer time.

ANALYSIS OF INSULATION

The total insulation for each baby was estimated by summing the individual contributions of each item of clothing and bedding. Tog values of materials similar to those found in the survey were measured by the method described in British Standard 4745.[11] (The tog is a unit of thermal resistance, one tog being 10 times the temperature difference in °C between the surfaces of a material when the heat flow through it is 1 watt/m^2.) The insulation contributed by each item was calculated from the tog value of its material and the proportion of the body, excluding the head, that it covered (table 2). For duvets, which vary widely in tog rating, the value for the individual brand was ascertained in accordance with British Standard 5335.[12] If

Department of Child Health, Medical School, University of Newcastle upon Tyne
C J Bacon
S A Bell
A B Beattie

British Textile Technology Group, Manchester
E E Clulow

Correspondence to:
Dr C J Bacon,
Friarage Hospital,
Northallerton,
North Yorkshire DL6 1JG.

Accepted 21 January 1991

Table 2 Amount of insulation contributed by each item of clothing and bedding, and proportion of surface area covered (excluding the head)

	Thermal resistance of fabric (tog)	*Proportion of surface area covered (excluding head)*
Clothing:		
Sleeping suit without hood	4·0	1·00
Babygro with feet	1·0	0·91
Quilted jacket	2·0	0·5
Cardigan	2·0	0·45
Tee-shirt	0·8	0·45
Vest	0·2	0·38
Tights	0·8	0·45
Dungarees	0·4	0·56
Socks	0·2	0·09
Mittens	2·0	0·10
Nappies:		
Terry nappy as worn, dry	3·5	0·19
Terry nappy as worn, wet	0·4	0·19
Disposable nappy, dry	4·0	0·19
Disposable nappy, wet	0·4	0·19
Bedding:		
Sheet	0·2	1·0
Blanket	1·5	1·0
Duvet	4–13·5	1·0

items were doubled, twice their tog value was taken.

STATISTICAL METHODS

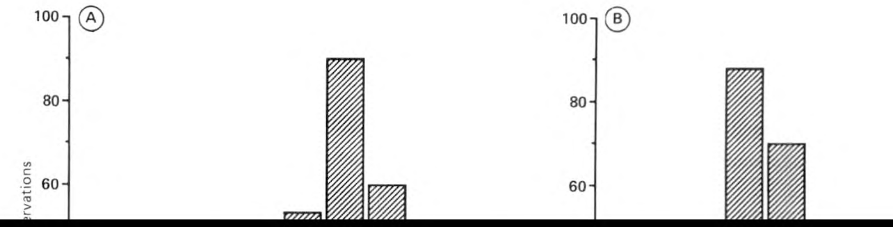
The mean (SEM) temperature and insulation for different groups were compared. Significance was usually assessed by Student's *t* test, paired where appropriate. Two way analysis of variance was done where appropriate. The association between temperature and insulation was examined by comparison of the mean insulations for a series of temperature ranges; regression analysis was not done because the association was not linear or sequential.

Results

AMBIENT TEMPERATURE AND HEATING

The distributions of ambient temperature near the baby's sleeping place at night in winter and summer are shown in fig 1. Modal values for minimum and maximum temperatures were 15°C and 20°C in winter, and 19°C and 23°C in summer.

During winter 76 (23·5%) babies' rooms were heated all night and 217 (66·9%) for part of it, and in summer 20 (6·1%) and 245 (75·4%), respectively. Figure 2 shows the association between outside temperature and minimum room temperature on winter nights, according to the presence and duration of heating. Regardless of heating, room temperature varied significantly compared with outside temperature ($p<0·01$, two way analysis of variance), though the difference between them was greater on colder nights. For a given outside temperature rooms heated all night were on average 4·2°C warmer, and rooms heated for part of the



[redacted]

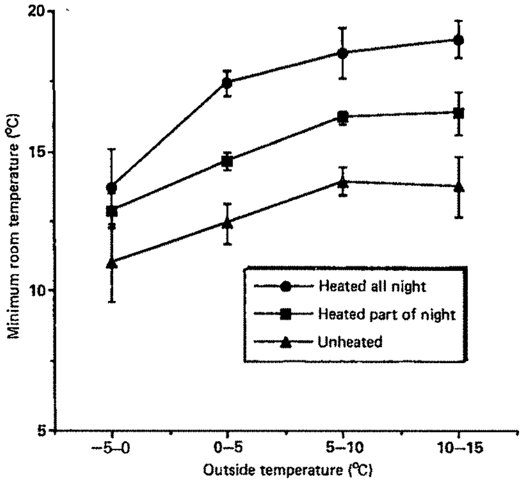


Figure 2 The association between outside temperature on winter nights and minimum temperature in heated and unheated rooms. Mean (SEM) room temperatures were calculated for each 5°C band of outside temperature.

night were 2·2°C warmer, than rooms with no heating at all.

Of the total, 190 babies (29·3%) slept in their own bedrooms at night, 442 (68·1%) shared their parents' bedrooms, and 15 (2·3%) slept in living rooms. The temperature in separate and shared bedrooms were similar, but living rooms were usually warmer than bedrooms, the mean maximum temperature being significantly higher (23·93 (1·21)°C compared with 20·45 (0·13)°C, $p<0·01$).

Only 83 mothers (12·8%) left windows open in their babies' rooms at night, being more likely to do so if the rooms were warmer; 200 babies' rooms (30·9%) were totally unventilated at night with windows and doors closed. On winter nights 70 mothers (21·7%) and on summer nights 23 (7·1%) heated the cot before putting the baby down to sleep, for example with an electric blanket or a hot water bottle.

INSULATION

The means and ranges for total insulation from clothing and bedding put on by day and night in summer and winter are shown in table 3. The contribution made by clothing was proportionally greater by day when babies were often put down to sleep wearing most of their clothes but with less bedding. Figure 3 shows the association of total insulation on winter nights to outside temperature and to maximum and minimum room temperature. Significantly less total insulation was applied when outside temperatures and when minimum room temperatures were higher (both $p<0·01$, two way analysis of variance). Within this overall relationship, however, there were wide variations between individuals subjects in the amount of insulation applied at the same ambient temperature. The variance was greater in colder weather. The extreme example of variation was provided by two mothers who put on 3·2 tog and 42·0 tog, respectively, for the same minimum room temperature. There was no significant association between total insulation and maximum room temperature at night; indeed, mean insulation was comparatively high for the babies with the warmest rooms.

The extent to which mothers allowed for room heating when deciding how much to insulate their babies varied (table 4). Babies who slept in living rooms tended to be covered a little more than those who slept in bedrooms (14·4 (1·36) compared with 13·50 (0·2) tog).

Figure 4 shows how, for a given room temperature, mothers put on more insulation on

Table 3 Mean (SEM) and range of tog values contributed by clothing and bedding according to season and time

	Summer (n=326)		*Winter (n=323)*	
	Day	*Night*	*Day*	*Night*
Total insulation of clothing and bedding (tog):				
Mean (SEM)	8·71 (0·29)	11·98 (0·25)	10·31 (0·25)	15·1 (0·29)
Range	2·4–22·8	3·2–28·2	2·2–31·4	3·2–42·0
Mean (SEM) contribution of clothing (tog)	4·35 (0·07)	3·58 (0·02)	4·86 (0·06)	4·56 (0·03)

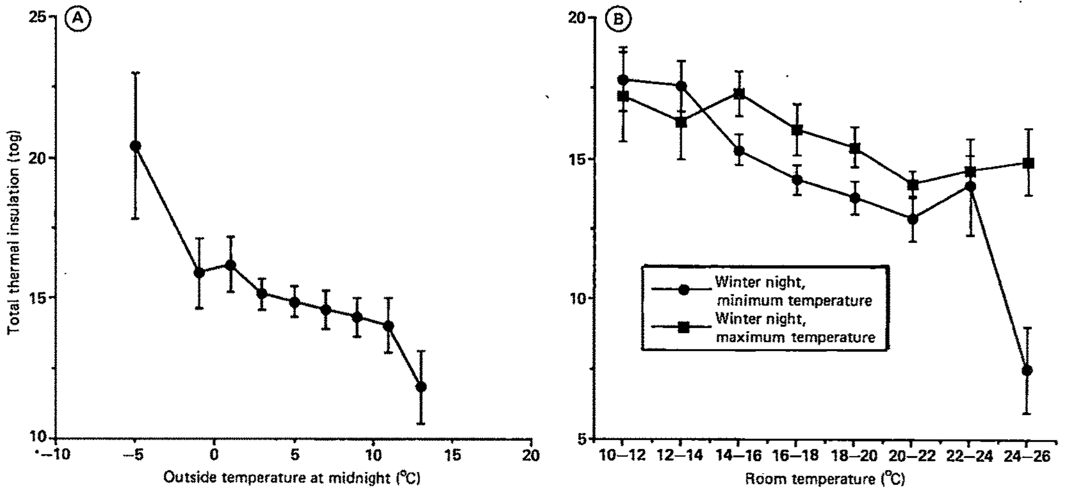


Figure 3 The association between total thermal insulation of sleeping babies on winter nights and (A) outside temperature at midnight; (B) maximum and minimum room temperatures. Mean (SEM) values for insulation were calculated for each 2° temperature band.

Table 4 Insulation and outside temperature in heated and unheated rooms on winter nights. Figures are expressed as mean (SEM) tog value

Outside temperature (°C)	*Room not heated*	*Room heated part of night*	*Room heated all night*
0–5	18·09 (1·56)* (n=7)	15·89 (0·56) (n=107)	14·44 (0·66)** (n=39)
5–10	14·56 (1·25) (n=17)	14·48 (0·48) (n=80)	13·39 (1·1) (n=19)
10–15	15·05 (1·18)* (n=4)	15·16 (1·27) (n=10)	11·05 (0·92)** (n=8)

* and **=p<0·01.

In 28 other cases the outside temperature was not within the range 0–15°C.

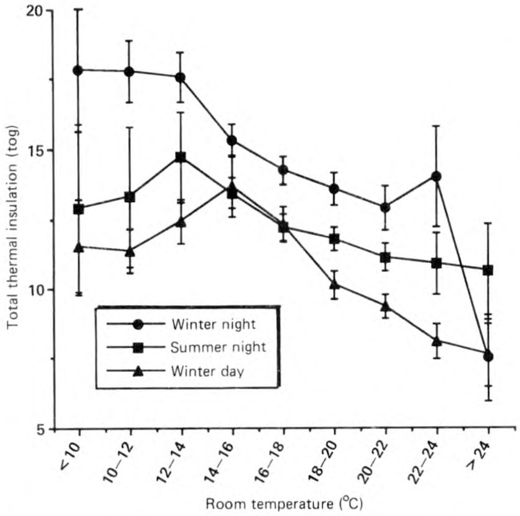


Figure 4 The association between total thermal insulation and room temperature on winter nights, summer nights, and winter days. Mean (SEM) values for insulation were calculated for each 2°C temperature band.

winter nights than they did either for summer

tucked their babies in tightly, and 15 (2·3%) usually took the babies into their own beds for most of the night.

EFFECT OF BABIES' GESTATION, AGE, AND BIRTH WEIGHT

Mothers made no special allowance in their covering or heating of the 37 babies who had been born prematurely (gestation <37 weeks). When the three age groups (roughly 8, 16, and 26 weeks) were compared, younger babies tended to have warmer rooms but less insulation on both winter and summer nights (fig 5). Babies with lower birth weights also tended to have warmer rooms but less insulation—for example, the 43 babies with birth weights <2500 g had a mean (SEM) minimum room temperature of 17·72 (0·4)°C and mean insulation of 12·72 (0·68) tog compared with 16·65 (0·44)°C and 14·22 (0·65) tog for the 52 who weighed >4000 g at birth (p<0·05 in each case).

SWEATING

Of the total, 183 mothers (28·2%) said that their babies usually sweated when asleep at night, 27 of them (4·2%) sweating profusely; and by day the figures were 149 (23·0%) and 12 (1·8%), respectively. There was no differences in the incidence of sweating among babies in different age groups; the same babies tended to sweat by night as by day. At night, babies sleeping in rooms with above average minimum temperatures were significantly more likely to sweat (p<0·001), but those sleeping under more than average total insulation were not.

ADJUSTMENTS FOR ILLNESS

[redacted]

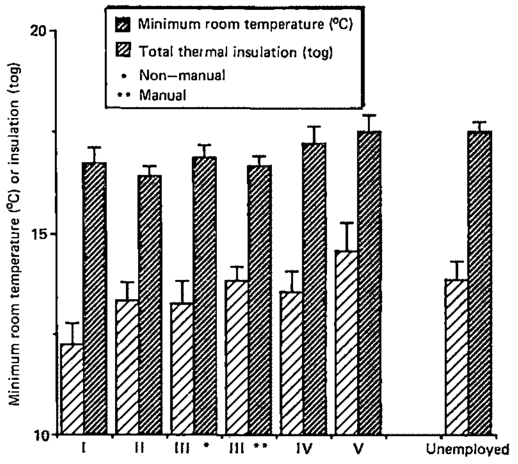


Figure 6 Minimum room temperature and total thermal insulation for babies in families of different social classes subdivided according to father's occupation. When he was unemployed the family was classified both by the last occupation, and as unemployed.

(81·4%) said that they would put on less covering, 36 (15·2%) said that they would decrease the heating, and 63 (26·6%) said that they would give the baby antipyretic medication.

ASSOCIATIONS WITH MATERNAL AGE, PARITY, AND EDUCATION

Mothers in all age groups kept their babies' rooms at about the same temperature. Younger mothers put on significantly more bedding than older mothers; the mean total insulation used by the 39 mothers under 20 years old was 15·1 (1·0) tog, compared with 12·1 (0·6) tog used by the 53 mothers over 35 years ($p<0·01$). Younger mothers were also more likely to keep their babies warmer when ill. There were no differences in room temperature or insulation used by mothers of different parity, but experienced mothers were more likely to keep their babies cooler when they were ill. The way mothers kept their babies warm was also related to duration of education: those who had left school at the age of 16 ($n=377$) used significantly more insulation ($p<0·05$) and slightly higher room temperatures than those whose education had continued after the age of 19 ($n=121$).

ASSOCIATION WITH OCCUPATIONAL GROUP

The variation in thermal environment at night with occupational group is shown in fig 6. Families in the lower groups tended both to keep their babies' rooms warmer at night and to put on more covering, as did families in which the father was unemployed. The differences in insulation between group I and groups II, III, and IV, and between group V and groups I, II, and III (non-manual) were significant ($p<0·05$). About the same proportion of families in each group had some form of heating in the baby's bedroom, or kept it on all night, or had a window open. Duvets were used to a similar extent in all groups, but many more mothers in the manual groups swaddled their babies. There were no differences among the groups in adjustments that were made for illness, or in the practice of having the baby in the parents' bed.

Discussion

We think that this is the most comprehensive study of babies' thermal environment yet published. Despite the high non-response rate and consequent skewed distribution of social classes, we have no reason to suppose that our sample was not representative with regard to the practices being studied, and the numbers were sufficient to allow analysis of each social group separately.

Table 5 shows how our figures for ambient temperatures compare with those reported from elsewhere. Mean room temperatures on winter nights in Newcastle, despite its cooler climate, were higher than those found in Leicester or Dunedin, which suggests that mothers in Newcastle used more heating. The differences in mean room temperatures in Newcastle between day and night and between summer and winter were not large, probably because heating damped down fluctuations with outside temperature. Paradoxically the highest room temperature (30°C) was recorded on a winter night and the lowest (4°C) by day.

As yet there is no standard method for assessing the insulating effect of babies' clothing and bedding. The method we have used does no more than quantify clothing and bedding on the trunk and limbs and does not attempt to calculate the effective physiological insulation of the whole body. Even in this limited aim we have had to disregard a number of factors including insulation from pillow, underbedding, and mattress; the reduction in insulating properties of items that have been much used and washed, or

Table 5 Reported ambient temperatures for sleeping babies

Place and year	*No of babies*	*Age (weeks)*	*Season*	*Time*	*Ambient temperature (°C)*		
					Range	*Mean*	*Mode*
Exeter 1984[6]	199	3–6	Winter	Day	10–25	17·9	Not recorded
Nottingham 1985[7]	200	4–26	Summer and winter	Day	16–29	21·2	20
Leicester 1985[8]	74	9–20	Winter	Night:			
				Bedtime	14–25	18·4	20
				Six hours later	7–23	14·0	17
Dunedin 1986[9]	276	4–6	Winter	Night:			
				Maximum		18·2	Not recorded
				Minimum	6·0–19·8	13·7	Not recorded
Newcastle 1985–7 (present study)*	324	8–26	Summer	Day	8–27	19·7	21
				Night:			
				Maximum	14–29	21·2	23
				Minimum	9–26	18·1	19
	322	8–26	Winter	Day	4–27	18·3	19
				Night:			
				Maximum	7–30	19·8	20
				Minimum	5–28	15·6	15

*Temperature recordings not available for three babies.

have been wetted by urine or by sweat; and the effect of the compression of individual layers of bedding. Calculation of the effective physiological insulation of the whole body is complex and needs to take into account various additional factors such as differential heat loss from different parts of the body, especially the uncovered head; the effect of posture; heat loss through curved surfaces; variations in the effectiveness of sweating with materials of varying permeability; and the insulation provided by the boundary layer of air.

The only other study to use the same method of quantification as ours was that done in Leicester which dealt with winter nights only: the mean value for insulation reported was 14·7 tog, which was similar to our value of 15·1 tog.[8]

The influence of social background on the way babies are kept warm differs between England and New Zealand. In Newcastle, as in Exeter[6] and Leicester (MP Wailoo, personal communication), families in the lower occupational groups kept their babies warmer, with hotter rooms and more bedding, whereas in Dunedin they kept them cooler, with colder rooms and less bedding.[9]

Because little is known about thermoregulation in this age group, ideal combinations of ambient temperature and insulation are not established, and there is a lack of informed advice for mothers. Our findings suggest that in consequence there is much inconsistency and sometimes illogicality in how mothers keep their babies warm. For a given room temperature they tend to put on more bedding by night than by day, and more in winter than in summer, which suggests that they are influenced more by their traditions and expectations for the time and the season than by objective assessment of ambient temperature. Often they do not make adequate allowance for room heating. At outside temperatures between 5°C and 10°C, for example, although rooms heated all night were on average 4·2°C warmer than unheated rooms, babies in the former had a mean of only 1·2 tog less covering than those in the latter. Similarly, babies who slept in the living room were insulated a little more than babies who slept in bedrooms, although living rooms were generally much warmer. Many mothers did not seem to appreciate that some makes of duvet confer a high degree of insulation, and that duvets are intended as a substitute for and not as an addition to other bedding. It is likely that the widespread introduction of both central heating and of duvets has resulted in sleeping babies being kept much warmer today than in previous generations. The high degree of insulation found at the highest maximum room temperature (fig 3) suggests that there may be a subgroup of mothers who are particularly concerned about keeping their babies warm. Many babies throw off their bedding, and it is possible that they do so because they feel too hot, in which case swaddling or tucking in tightly may deprive them of a beneficial manoeuvre.

It may at first seem surprising that younger and smaller babies, whose greater surface: mass ratio makes them more vulnerable to heat loss, were given less insulation than older and larger babies. This was compensated for by a higher ambient temperature, however, so that the balance of their thermal environment was more like the one that they had experienced in the hospital nursery.

Thirty years ago attention was drawn to the dangers of hypothermia in babies, and mothers were rightly advised to avoid letting their babies get cold.[13] The lesson seems to have been well learnt, and the OPCS now records few deaths in infancy from this cause.[14] Has the pendulum now swung too far the other way so that babies are less at risk from cold than from excessive efforts to avoid it?

The babies in our study who were kept warmest did not seem any the worse for it except that some of them sweated, which suggests they may have been under thermal stress. The possibility remains, however, that a high level of insulation that is tolerable in normal circumstances may be dangerous if some other factor intervenes. For example, the baby may rapidly develop a fever, or may slip beneath the coverings so that the main channel for losing surplus heat, through the uncovered head, is lost.[15] It may be relevant that some of the factors we found to be associated with higher levels of heating and insulation (younger mothers, lower social group, winter season, night) are also associated with SIDS.[16] Our data offer some support for the hypothesis of 'paradoxical overheating'—babies may be more at risk of hyperthermia when it is cold.

It is vital that these issues are clarified, because if overheating is indeed a contributory factor to some cases of death or damaging illness it would be entirely preventable by soundly based advice to mothers.

This survey was funded by the Foundation for the Study of Infant Deaths. We thank Dr EN Hey and Professor A Aynsley-Green for their advice and support, and the mothers who answered our questionnaire.

1 Stanton AN, Scott DJ, Downham MAPS. Is overheating a factor in some unexpected infant deaths? *Lancet* 1980;i:1054–7.
2 Stanton AN. Overheating and cot death. *Lancet* 1984;ii:1199–201.
3 Nelson EAS, Taylor BJ, Weatherall IC. Sleeping position and infant bedding may predispose to hyperthermia and the sudden infant death syndrome. *Lancet* 1989;i:199–201.
4 Fleming PJ, Gilbert R, Azaz Y, *et al*. The interaction between bedding and sleeping position in sudden infant death syndrome: a population-based controlled study. *BMJ* 1990;**301**:85–9.
5 Bacon C, Scott D, Jones P. Heastroke in well-wrapped infants. *Lancet* 1979;i:422–5.
6 Eiser C, Town C, Tripp J. Dress and care of infants in health and illness. *Arch Dis Child* 1985;**60**:465–70.
7 Nicoll A, Davies L. How warm are babies kept at home? *Health Visitor* 1986;**59**:113–4.
8 Wailoo MP, Petersen SA, Whittaker H, Goodenough P. The thermal environment in which 3–4 month old infants sleep at home. *Arch Dis Child* 1989;**64**:600–4.
9 Nelson EAS, Taylor BJ. Infant clothing, bedding and room heating in an area of high postneonatal mortality. *Paediatric and Perinatal Epidemiology* 1989;**3**:146–56.
10 Office of Population Censuses and Surveys. *Classification of occupations*. London: HMSO, 1980.
11 BS 4745. *Method for the determination of thermal resistance of textile materials*. London: British Standards Institute, 1986.
12 BS 5335. *Specification for continental quilts*. London: British Standards Institute, 1984.
13 Bower BD, Jones LF, Weeks MM. Cold injury in the newborn. *BMJ* 1960;i:303–9.
14 Office of Population Censuses and Surveys. *Mortality statistics: cause. 1976–85*. London: HMSO, 1987.
15 Anderson ES, Wailoo MP, Petersen SA. Use of thermographic imaging to study babies sleeping at home. *Arch Dis Child* 1990;**65**:1266–7.
16 Golding J, Limerick S, Macfarlane A. *Sudden infant death: patterns, puzzles and problems*. Shepton Mallet: Open Books, 1985.

Archives of Disease in Childhood 1991; **66:** 633–635

Delay in diagnosis of childhood asthma and its influence on respiratory consultation rates

Ian Charlton, Kevin Jones, John Bain

Abstract

A survey of cases of asthma in two general practices with a special interest in the disease identified 212 asthmatic children aged 0–16 years by the end of January 1989 who had been registered in that practice since birth. Delay in diagnosis, both in terms of time (median 2·95 years) and number of consultations (median 7), was considerable. Annual rates of consultations for respiratory symptoms that were initiated by the patients fell significantly after diagnosis (median before=1·80, after=0·95 consultations/year), but the number initiated by the doctors rose significantly (median before=0, after=1·01 consultations/year). The overall rates before and after diagnosis were not significantly different (median before=2·04, after=2·21 consultations/year). Increased efforts are required to reduce this delay thereby minimising the morbidity of asthma in childhood.

The underdiagnosis of asthma in children was first highlighted by Speight in 1978.[1] Since then Levy and Bell have shown that even in their practice, which has a special interest in asthma, the median category of number of consultations for respiratory symptoms before a diagnosis of 'asthma' was made was 16–20[2]; the mean time between first respiratory consultation and diagnosis was 50·4 months (M Levy, personal communication). Jones and Sykes found a diagnostic delay of roughly 40% of the child's age.[3]

In this study we have examined delay in diagnosis, both in terms of time and numbers of consultations, and rates of consultation for respiratory symptoms before and after diagnosis.

Subjects and methods

Two practices with a special interest in asthma were studied: the urban practice of 8100 patients attached to the University Primary Medical Care Group in Southampton, and a training practice of 7990 patients in Aylsham, Norfolk. Only those children aged under 16 years who had been registered since birth were included. Disease registers were used to identify the asthmatic children in this group. For each eligible asthmatic child the date of birth, date of first respiratory consultation, date of diagnosis of asthma, and the number of consultations for respiratory symptoms before and after diagnosis (up to the end of January 1989), were recorded.

These consultations were divided into those initiated by the patient and those initiated by the doctor. Those initiated by the patient were defined as those consultations at which the patient had been recorded as presenting with one or more of the following: cough, wheeze, upper or lower respiratory tract infection, or sleep disturbed by coughing. Respiratory consultations initiated by the doctor were defined as those in which review was mentioned in the notes, those at a prescribed time after a previous visit (for example, 'see in two weeks'), or those where respiratory symptoms were reviewed when the patient attended for some other reason.

Delay in diagnosis was calculated by subtracting the age of first consultation for respiratory symptoms from that at which the word 'asthma' first appeared in the notes. The number of such consultations before diagnosis included both the first consultation and that at which the diagnosis was made. Annual rates for both types of consultation were calculated before diagnosis for patients whose delay in diagnosis was at least one year, and after diagnosis for those whose diagnosis had been made at least 12 months previously. This period was chosen for two reasons: firstly, to avoid the more recent period in which asthma clinics run by nurses were operating in both practices, and secondly, to avoid calculating annual rates based on less than one year's data. Rates before diagnosis were calculated by dividing the number of consultations up to and including that at which the diagnosis of asthma was made by the delay in diagnosis. Rates after diagnosis were calculated by dividing the number of respiratory consultations since diagnosis by the period between diagnosis and the end of the study. Data were analysed using the Statistical Package for the Social Sciences (SPSS) PC package for IBM compatible personal computers[4] and the Confidence Interval Package of Gardner *et al.*[5] The annual rates before and after diagnosis were compared by the Wilcoxon matched pairs signed rank test.

Results

A total of 212 children (123 boys and 89 girls) fulfilled the criteria for entry, 112 from Aldermoor and 100 from Aylsham. This gives a lifetime prevalence of asthma of 11% for Aldermoor and 10% for Aylsham. Table 1 shows the number of diagnoses of asthma made in 168 children diagnosed before the age of 8 years according to the year of diagnosis. This shows the time trend in the diagnosis of asthma for these younger children during the study period.

The median delay in diagnosis for the whole

Primary Medical Care Group, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton SO1 6ST
Ian Charlton
Kevin Jones
John Bain

Correspondence to:
Dr Charlton.

Accepted 15 January 1991

Table 1 Time trend in diagnosis of asthma in 168 children aged ≤8 years

Year of diagnosis	*Age at diagnosis (years)*	
	0–4	*4–8*
1973–6	2	0
1977–80	5	7
1981–4	20	25
1985–8	55	54
Total	82	86

Table 2 Annual respiratory consultation rates before and after the diagnosis of asthma

	Annual consultation rate	
	Mean (SD)	*Median (interquartile range)*
Before diagnosis (n=158, delay in diagnosis at least one year):		
Consultations initiated by patient	2·29 (1·72)	1·80 (1·04–3·03)
Consultations initiated by doctor	0·31 (0·66)	0 (0–0·34)
Total consultations	2·60 (2·08)	2·04 (1·10–3·12)
After diagnosis (n=156, time since diagnosis at least one year):		
Consultations initiated by patient	1·38 (1·36)	0·95 (0·41–1·86)
Consultations initiated by doctor	1·46 (1·42)	1·01 (0·43–2·03)
Total consultations	2·84 (2·36)	2·21 (1·11–4·12)

group of 212 children was 2·95 years (95% confidence interval (CI) 2·58 to 3·69) with the median number of consultations before diagnosis being 7 (95% CI 6 to 8). The median age at first presentation with respiratory symptoms was 0·8 years (95% CI 0·69 to 1·02). The rates of consultations initiated by the doctor and by the patient, and the total consultation rates for respiratory complaints before and after the diagnosis of asthma for the 158 children whose diagnosis had been delayed at least one year, and for the 156 children who had been followed up for at least one year since diagnosis are shown in table 2.

In the 120 cases in which there had been a delay in diagnosis of more than a year, and a time since diagnosis of more than a year, the rate of consultations initiated by the patient after diagnosis was significantly less than it had been before diagnosis (z=−6·13, p<0·0001), but the rate initiated by the doctor after diagnosis was significantly greater than it has been before diagnosis (z=−7·94, p<0·0001). There was no significant difference between the total rate before and after diagnosis (z=−0·56, p=0·58).

Discussion

Although our study—which was done in 1989—cannot be compared directly with that of Levy and Bell (published in 1984),[2] our results do indicate a trend towards a reduction in the total time period and the number of consultations for respiratory symptoms that occurred before the diagnostic label of 'asthma' is used in practices with an interest in the disease. The delay still remains substantial, however.

Does this delay matter? Firstly, our definition of delay must be somewhat arbitrary, because children may present with respiratory symptoms before they truly have 'asthma', which may exaggerate the period of real delay. Howie argued that general practitioners tend to proceed from symptoms to treatment without necessarily making a diagnosis.[6] This is because general practitioners are often dealing with the early symptoms and signs of undifferentiated problems and precise diagnostic labels are often not justified. The importance of the label 'asthma' in ensuring correct treatment has, however, been clearly shown.[7]

In 1978 Speight examined 34 unselected patients who were referred to paediatric outpatient clinics in Newcastle and London and were diagnosed as having asthma.[1] In only two children had asthma been diagnosed before referral, but most showed appreciable clinical improvement after diagnosis. He highlighted three factors that seemed to militate against the diagnosis of asthma being made in general practice. These were: parents' choice of symptoms, overemphasis on the role of infection, and reluctance to use the word 'asthma'.

In 1983 Speight *et al* conducted a large survey of 7 year old children at school in North Tyneside.[8] Of 2700 children, 279 were reported by parents to have had a history of wheeze since they went to school. A sample of about two thirds (n=179) was studied further. Only 21 had been diagnosed as having asthma, six after referral to hospital. Only a third of those who had more than 12 episodes of wheezing a year had been diagnosed as having asthma. By the end of the survey 31 children who were receiving prophylaxis had considerably reduced the amount of time that they spent off school.

A similar survey of 8 year olds in London was done in 1981 by Anderson *et al*; this also showed that wheezy children were being undertreated.[7] Those said to have asthma were significantly more likely to have used antiasthmatic drugs than those who were not (56/94 compared with 8/185).

Our data have shown an almost exponential rise in the number of cases of asthma diagnosed, which although not related to total numbers of children in the practices, represents a substantial change in the diagnostic behaviour of the general practitioners concerned. From the available evidence, this increase should have resulted in a greater use of appropriate treatment and a possible reduction in morbidity. Further reduction in the substantial delays in diagnosis may increase this effect. There is likely, however, to be a period of delay during which the potential benefits of early treatment of asthma are outweighed by the risks of engendering anxiety and overtreatment. The magnitude of this 'optimal delay' is unknown.

Our results did not show that diagnosing asthma in a child reduces the total number of consultations for respiratory symptoms, but the desired endpoint is reduced morbidity, not reduced workload. It can be inferred, albeit indirectly, that some reduction in morbidity did occur after diagnosis, as rates of consultations initiated by the doctor (proactive) rose significantly and those initiated by the patient (reactive) fell significantly. This implies that some reactive or acute presentations may have been prevented by proactive care. To be certain that reducing diagnostic delay in childhood asthma in general practices leads to lowered morbidity requires a lengthy study relating delay to morbidity over time in that setting.

Clearly, merely labelling a child as 'asthmatic' cannot reduce morbidity, but if the application of the label leads to improved care in terms of greater attention to inhaler technique, proactive follow up by the nurse or doctor, the development of self management skills, and better explanation to parents, morbidity should be reduced. The nature of general practice may permit proper management of illnesses without precise diagnostic labelling, but we feel confident in recommending that in childhood asthma increased efforts should be made in primary care to further reduce diagnostic delay.

We thank Mark Mullee, senior statistical programmer, department of medical statistics and computing, University of Southampton, for help with the analysis, and the following members of the primary medical care group, Southampton University: Samantha Smith for help in data processing and Dr Roger Jones and Dr Ann-Louise Kinmonth for their encouragement and advice.

1 Speight ANP. Is childhood asthma being underdiagnosed and undertreated? *BMJ* 1978;ii:331–2.
2 Levy M, Bell L. General practice audit of asthma in childhood. *BMJ* 1984;**289**:1115–6.
3 Jones A, Sykes A. The effect of symptom presentation on delay in asthma diagnosis in children in a general practice. *Respiratory Medicine* 1990;**84**:139–42.
4 Norusis MJ. The Statistical Package for the Social Sciences (SPSS) guide to data analysis for SPSS/PC+. Chicago: SPSS Inc, 1989.
5 Gardner MJ, Gardner SB, Winter PD. *Confidence interval analysis (CIA), microcomputer program manual.* London: British Medical Association, 1989.
6 Howie JGR. Diagnosis—the Achilles heel? *J R Coll Gen Pract* 1972;**22**:310–5.
7 Anderson HR, Bailey PA, Cooper JS, Palmer JC. Influence of morbidity, illness label and social, family and health service factors on drug treatment of childhood asthma. *Lancet* 1981;ii:1030–2.
8 Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *BMJ* 1983;**286**:1253–5.

Bird attack and campylobacter

Campylobacter jejuni is the commonest enteric bacterial pathogen in England and Wales. Most cases are sporadic and the source of infection is usually unknown but an outbreak in South Wales in May 1990 may have been caused by the contamination of milk by birds (Southern *et al*, *Lancet* 1990;**336**:1425–7).

In a case-control study involving 32 cases and 64 controls significantly more cases reported that their milk bottles had been attacked by birds especially in the week before the onset of illness. Controls were less likely to have their milk delivered to the door and more likely to have discarded milk from attacked bottles or to have taken measures to protect the bottles from birds.

The suspected birds are magpies and jackdaws. *Campylobacter* spp have been grown from the beaks and cloacae of these birds. You can hazard a guess at what kind of bird has been at your milk by looking at the bottle top. Tits, it seems, peck holes in the shiny bottle top but magpies tear off the top completely.

How many paediatricians know that the word pica is taken from the latin for magpie (*Pica pica*)? Alfred Hitchcock devotees, of course, have known for a long time that the birds are out to get us.

ARCHIVIST

Archives of Disease in Childhood 1991; **66:** 636–637

Septicaemia and adrenal haemorrhage in congenital asplenia

M P Dyke, R P Martin, P J Berry

Abstract

Five patients developed overwhelming infection as a result of congenital asplenia, which was previously unsuspected in all cases. Each illness followed a fulminant course resulting in death within 24 hours. They illustrate the respective roles of *Haemophilus influenzae* infection (n=4) and adrenal haemorrhage (n=4) in this condition. We suggest a management protocol for screening infants with abnormalities of the atria or viscera with splenic ultrasound and examination of a blood film for Howell-Jolly bodies. Vaccination and prophylactic antibiotics should be considered for those at risk. Vigorous use of parenteral antibiotics and steroids in suspected infection is recommended.

Congenital asplenia, or polysplenia, may occur in isolation, or as one of several abnormalities of the heart and viscera.[1–5] Two main groups of abnormality have been described. Asplenia may be associated with right isomerism, which presents as bilateral trilobed lung and situs inversus of abdominal organs. Polysplenia may occur with left isomerism, bilateral bilobation of the lung, and abdominal heterotaxy.[5–7]

Over 90% of cases are associated with complex congenital heart disease,[5] and the high mortality rate in the early months of life has been largely attributable to this.[5 8] As surgical techniques and supportive care improve, however, many more children with severe heart disease can be expected to survive the first few months.[9] Waldman *et al* found that infants with asplenia who survived the first month were more likely to die from sepsis than from their heart disease.[8] Several reports have described sepsis in asplenic patients and a number of consistent features emerge.[8 10–15] Infecting organisms are usually pneumococcus or *Haemophilus influenzae*. The course of the illness is commonly fulminant with the rapid onset of hypovolaemic shock, disseminated intravascular coagulopathy, and loss of consciousness. Mortality is extremely high, being at least 50% in all series and greater than 80% in many. It is, therefore, becoming increasingly important to seek out evidence of anatomical or functional hyposplenia and to institute measures to protect those infants at risk from overwhelming infection.

We describe five patients who presented to the Bristol Children's Hospital between 1982 and 1990 in whom hyposplenism was not previously suspected and whose illnesses were fulminant and ultimately fatal.

Royal Hospital for Sick Children,
St Michael's Hill,
Bristol BS2 8BJ
Institute of Child Health
M P Dyke
R P Martin

Department of Pathology
P J Berry

Correspondence to:
Dr Dyke.

Accepted 14 January 1991

Case reports

CASE 1

A previously well 2 year old boy presented with 24 hours of fever followed by diarrhoea and rigors. Rectal temperature was 40°C and he was centrally cyanosed with tachypnoea, tachycardia, and unrecordable blood pressure. Despite being given antibiotics, plasma, and methyl prednisolone he died eight hours after admission.

Necropsy showed no abnormality except for an extremely small spleen (10 g) and bilateral adrenal haemorrhage. *H influenzae* type B was cultured from the blood.

CASE 2

A baby girl who was known to have right atrial isomerism, double inlet and double outlet indeterminate ventricle, a complete atrioventricular septal defect with common atrioventricular valve, and pulmonary stenosis presented at 3 months of age with a simple upper respiratory infection that lasted for 10 days and culminated in acute cardiovascular collapse. She died from cardiac and renal failure within 24 hours of admission to hospital despite full support including peritoneal dialysis.

Necropsy confirmed the cardiac abnormalities and showed that she had no spleen, her stomach and pancreas were on the right, and she had a narrow midline mesenteric root. She also had bilateral adrenal haemorrhages and *H influenzae* type B was subsequently cultured from her blood.

CASE 3

A 15 month old child presented with a few hours' history of vomiting and fever, followed by loss of consciousness and a single generalised convulsion. There was no localised infection but dextrocardia was noted. Antibiotics and full supportive treatment were started, but the child had a cardiac arrest and resuscitation was unsuccessful. *H influenzae* type B was cultured from blood and cerebrospinal fluid.

Necropsy showed thoracic and abdominal situs inversus. There were small splenunculi in the right upper quadrant of the abdomen and both adrenal glands were haemorrhagic.

CASE 4

A baby girl was found to have dextrocardia with right atrial isomerism, ambiguous atrioventricular connection, complete atrioventricular septal defect with common atrioventricular valve, double outlet right ventricle, pulmonary valve stenosis, and bilateral superior vena cavas at birth. She remained well until 9 months of age when she presented with laboured respiration and cyanosis of sudden onset. Initial investigations showed no abnormalities except for a chest radiograph, which showed free gas under the diaphragm. She was treated with artificial ventilation, plasma, and antibiotics, but died shortly after admission.

Necropsy confirmed the cardiac abnormalities. Abdominal viscera were normal although the small bowel mesentery was narrow. There was necrotising gastritis with free peritoneal gas and fluid from which *Pseudomonas aeruginosa* was isolated. She had no spleen.

CASE 5

A previously fit 7 month old boy presented with a two hour history of fever and listlessness. Initial examination showed that he had a temperature of 37·6°C and respirations of 60/minute. Four hours later he collapsed; his skin became grey and mottled, and he developed tachycardia with increasing tachypnoea. Investigations showed no abnormality except for a relative neutropenia. He died six hours later despite treatment with artificial ventilation, inotropic agents, plasma, steroids, and antibiotics.

Necropsy showed a normal thoracic cavity but the liver and gall bladder were in the midline, and he had an annular pancreas and a narrow mesenteric root. Both adrenal glands were haemorrhagic and there was no spleen. *H influenzae* type B was subsequently cultured from the blood.

Discussion

Although the increased risk of bacterial infection in the asplenic host is well known, congenital asplenia is still largely unrecognised as a cause of sudden unexpected death in infancy.[8,10–15] Our series illustrates several important features of the problem. Firstly, there is an association with cardiac and other abnormalities. Two of our cases had complex lesions similar to those previously described,[1–7] and a third had dextrocardia. Viscera were abnormally placed in three. Secondly, *H influenzae* is an important pathogen, and was isolated from blood in four cases and from cerebrospinal fluid in one. Thirdly, the course of the illness is rapid and fulminant; no child survived 24 hours after acute collapse, and in three cases death followed less than 12 hours after the first symptoms. Finally, adrenal haemorrhage was found in four of the five cases.

THERAPEUTIC AND PROPHYLACTIC CONSIDERATIONS

Death of infection in a congenitally asplenic child is quick, and if it is to be prevented infection must be anticipated. This series focuses attention on the need for a comprehensive programme of screening with preventative and therapeutic measures to reduce the mortality. As the incidence of isolated congenital asplenia is low, screening should be limited to those children presenting with complex heart disease, particularly with atrial isomerism, and those with viscera sited abnormally in whom an ultrasound scan to assess splenic size and a blood film for Howell-Jolly bodies should be done.[16] An abnormality of either would be an indication for a ^{99m}Tc sulphur colloid scan.[17] The use of dodecavalent pneumococcal vaccine in the older patients who have had their spleens removed is well established and reduces the risk from pneumococcal infection, although its role in congenitally asplenic children is less certain.[18] In addition vaccination against *H influenzae* is now available and should be considered for younger asplenic children.

Antibiotic prophylaxis, traditionally with penicillin for older children without spleens,[8,13] should be with amoxycillin to offer protection against *Haemophilus* spp.[8] When amoxycillin resistance in *Haemophilus* spp is common or in cases of penicillin sensitivity, trimethoprim may be substituted. Perhaps the most important benefit of detection by screening would be the opportunity to institute early treatment with parenteral antibiotics in cases of suspected sepsis, with steroid supplements to avoid endotoxic and adrenal collapse.

1 Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood. *Acta Paediatrica* 1955;**44**(Suppl 104):1–110.

2 Gilbert EF, Nishimura K, Wedum G. Congenital malformation of the heart associated with splenic agenesis. *Circulation* 1958;**17**:72–83.

3 Freedom RM. The asplenia syndrome. A review of significant extracardiac structural abnormalities in 29 necropsied patients. *J Pediatr* 1972;**18**:1130–3.

4 Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. In: Bergsma D, ed. *Congenital cardiac defects—recent advances*. Birth defects: original article series. Baltimore: A R Liss 1982:36–44.

5 Rose V, Izukawa T, Moes CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. *Br Heart J* 1975;**37**:840–52.

6 Ruttenberg HD, Neufeld HN, Lucas RV, *et al*. Syndrome of congenital cardiac disease with asplenia. *Am J Cardiol* 1964;**13**:387–406.

7 Marceletti C, Di Donato R, Nijveld A, *et al*. Right and left isomerism: the cardiac surgeon's view. *Ann Thorac Surg* 1983;**35**:400–5.

8 Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS. Sepsis and congenital asplenia. *J Pediatr* 1977;**90**:555–9.

9 Di Donato R, di Carlo D, Squitieri C, *et al*. Palliation of cardiac malformations associated with right isomerism (asplenia syndrome) in infancy. *Ann Thorac Surg* 1987;**44**: 35–39.

10 Kevy SV, Tefft M, Vawter GF, Rosen FS. Hereditary splenic hypoplasia. *Pediatrics* 1968;**42**:752–7.

11 Dickerman JD. Bacterial infection in the asplenic host: a review. *J Trauma* 1976;**16**:662–7.

12 King K, Schumacher HB. Spenic studies I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg* 1952;**136**:239–42.

13 Lucas RV, Krivit W. Overwhelming infection in children following splenectomy. *J Pediatr* 1960;**57**:185–91.

14 Gopal V, Bisno AL. Fulminant pneumococcal infections in 'normal' asplenic hosts. *Arch Intern Med* 1976;**137**:1526–30.

15 Singer DB. Postsplenectomy sepsis. In: Rosenberg HS, Bolande RP, eds. *Perspectives in pediatric pathology*. Vol 1. Chicago: Year Book Medical Publishers, 1973:285–311.

16 Padmanabhan J, Risenberg HM, Rowe R. Howell-Jolly bodies in the peripheral blood of full term and premature neonates. *Johns Hopkins Medical Journal* 1973;**132**:146–7.

17 Treves S, Spencer RP. Liver and spleen scintigraphy. *Semin Nucl Med* 1973;**3**:55–8.

18 Biggar WD, Ramirez RA, Rose V. Congenital asplenia: immunological assessment and a clinical review of eight surviving patients. *Pediatrics* 1981;**67**:548–51.

Malignant osteopetrosis: hypercalcaemia after bone marrow transplantation

P S M Rawlinson, R H A Green, A M Coggins, I T Boyle, B E S Gibson

Abstract

A 3 year old girl presented with malignant osteopetrosis, which was treated by allogeneic bone marrow transplantation. Successful engraftment was complicated by prolonged hypercalcaemia, which was controlled by a combination of a bisphosphonate, phosphate infusions, vigorous resalination, and salmon calcitonin. She was alive and well 16 months after the transplant.

Case report

A female infant was born vaginally at term after an uneventful pregnancy to healthy unrelated parents. Development was normal until a squint was noted at 7 months. Subsequent radiological examinations showed that she had osteosclerotic bones. A bone marrow biopsy specimen showed osteopetrosis. At 36 months she received an allogeneic bone marrow transplant after preparation with cyclophosphamide and single fraction total body irradiation.

By day 34 her sustained neutrophil count was over $1\cdot0\times10^9$/l, and the adjusted serum calcium concentration was 2·56 mmol/l. This increased within 48 hours to 3·67 mmol/l (fig 1). Initial treatment consisted of methylprednisolone (40 mg/kg/day) and a forced diuresis of normal saline 3 l/m^2/day with boluses of frusemide (1 mg/kg). The hypercalcaemia persisted over the next two days and salmon calcitonin 60 IU/day was added to the regimen. Later the same day her level of consciousness decreased and she required assisted ventilation. The adjusted serum calcium concentration at this time was 4·07 mmol/l and her carbon dioxide tension was 13·8 kPa. The forced diuresis was increased to 4·5 l/m^2/day with frusemide 1 mg/kg/hr as a continuous infusion, and the salmon calcitonin was increased to 60 IU three times a day. She was dialysed against a low calcium dialysate (Renalyte S519, Macarthy's Laboratories, Romford) for three six hour periods during the next 48 hours. After each dialysis she was given 5 mg of aminohydroxypropylidene bisphosphonate (APD) intravenously. Despite these measures the serum calcium concentration remained above 3·67 mmol/l and she had prolonged episodes of bradycardia. Phosphate 10 mmol was given as an infusion over six hours, which reduced the serum calcium concentration to 2·54 mmol/l. The serum phosphate concentration increased from 2·06 to 3·70 mmol/l and returned to normal 24 hours after completion of the infusion. She was extubated three days later.

She had four further hypercalcaemic crises despite continuing treatment with salmon calcitonin 60 IU three times a day (fig 2). The last occurred 148 days after transplantation. Each was successfully controlled with a forced diuresis of 3 l/m^2 normal saline, a single dose of APD 5 mg, and an infusion of phosphate 5–10 mmol if the calcium concentration rose above 3·0 mmol/l.

At discharge, 178 days after the transplant, the adjusted serum calcium concentration was stable (2·6–2·9 mmol/l). A maintenance dose of salmon calcitonin 60 IU three times a day on alternate days was continued, and was reduced over the next four months.

Sixteen months after the transplant the hepatosplenomegaly had resolved, her neurological

Royal Infirmary, Glasgow G4 0SF
Department of Haematology
P S M Rawlinson

University Department of Medicine
I T Boyle

Department of Haematology, Royal Hospital for Sick Children, Glasgow
R H A Green
A M Coggins
B E S Gibson

Correspondence to:
Dr Rawlinson.

Accepted 12 December 1990
(*Arch Dis Child* 1991;66:638–9)

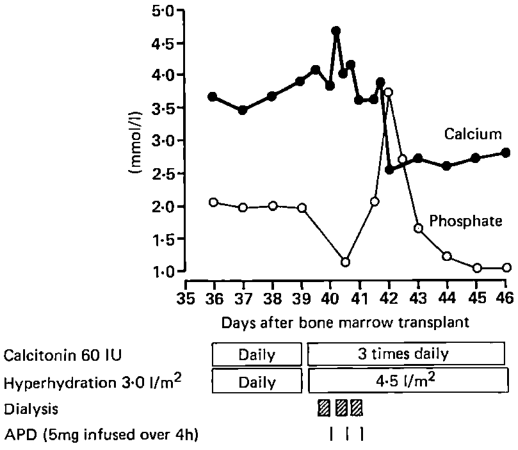


Figure 1 Response of serum calcium and phosphate concentrations to the treatment given during the first hypercalcaemic crisis.

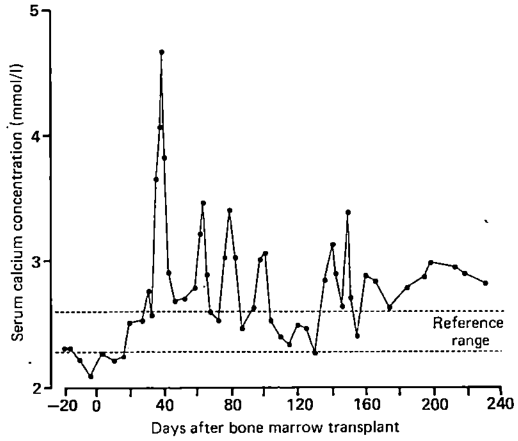


Figure 2 Serum calcium concentrations from 20 days before to 240 days after bone marrow transplantation (reference range 2·27–2·59 mmol/l).

abnormalities were no worse, and her osteosclerosis had improved both histologically and radiologically. The graft was intact and of donor origin. She was well, intellectually bright, and attending a preschool for the blind.

Discussion

In this case engraftment was followed by a rapid rise in the calcium concentration, and hypercalcaemia recurred on a number of occasions. A management plan to control the serum calcium concentration during these acute phases and to maintain long term normocalcaemia evolved with experience. In the acute phase the hypercalcaemia seemed to be controlled primarily by a combination of rehydration, intravenous phosphate infusions, and a bisphosphonate. Calcitonin was useful as a maintenance agent but was not completely effective alone.

Phosphate infusions produced a rapid, dose dependent reduction in the serum calcium concentration, which is directly related to the rise in the serum phosphate concentration.[1] The serum phosphate concentrations returned to their pretreatment values within 24 to 36 hours of the infusion. The risk of soft tissue calcification after a phosphate infusion is therefore likely to be short lived. In our patient there was no radiological evidence of soft tissue calcification or of nephrocalcinosis, despite repeated phosphate infusions.

APD is thought to be localised and concentrated in hydroxyapatite, making bone more resistant to osteoclastic activity[2]; to inhibit osteoclast formation from stem cells at low concentration[2]; and to have a direct antiosteoclast effect at high concentrations.[3] It should therefore be an effective drug in the management of hypercalcaemia after bone marrow transplantation for osteopetrosis as it would control osteoclast recruitment and activity. APD has not, to our knowledge, previously been used for this condition. The number of infusions required to regain control of the serum calcium became less with time, presumably reflecting the progressive reduction in total skeletal calcium load. Its long term use might, however, be associated with defects in mineralisation.[4] For this reason salmon calcitonin, given by subcutaneous injection, was used as maintenance treatment. There was an incomplete (but nevertheless clinically useful) response to calcitonin, and at one year after bone marrow transplant the need to suppress accelerated bone remodelling disappeared.

CONCLUSION

Successful engraftment of older children with osteopetrosis is often complicated by severe hypercalcaemia. Acute episodes of hypercalcaemia can be controlled by resalination together with APD given intravenously and a phosphate infusion. The latter, although rapid may introduce a risk of soft tissue calcification and nephrocalcinosis. Salmon calcitonin was useful for maintenance treatment.

We thank Dr SH Ralston for his help and advice.

1 Fulmer DH, Dimich AB, Rothschild EO, Laird Myers WP. Treatment of hypercalcaemia. Comparison of intravenously administered phosphate, sulfate, and hydrocortisone. *Arch Intern Med* 1972;129:923–30.

2 Boonekamp PM, van de Wee Pals LJA, van Wijk-van Lennep MLL, Thesing CW, Bijvoet OLM. Two modes of action of bisphosphonates on osteoclastic resorption of mineralised matrix. *Bone and Mineral* 1986;1:27–39.

3 Boonekamp PM, Lowik CWGM, van de Wee Pals LJA, van Wijk-van Lennep MLL, Bijvoet OLM. Enhancement of the inhibitory action on the transformation of osteoclast precursors into resorbing cells after demethylation of the amino group. *Bone and Mineral* 1987;2:39–42.

4 Cantrill JA, Anderson DC. Treatment of Paget's disease of the bone. *Clin Endocrinol* 1990;32:507–18.

Genetic aspects of admissions to a paediatric intensive care unit

D R FitzPatrick, C H Skeoch, J L Tolmie

Intensive Therapy Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ
D R FitzPatrick
C H Skeoch

Duncan Guthrie Institute of Medical Genetics, Glasgow
J L Tolmie

Correspondence to:
Dr Skeoch.

Accepted 7 January 1991

(*Arch Dis Child* 1991;66:639–41)

Abstract

Of 821 consecutive admissions to a paediatric intensive care unit, 47 (5·7%) were for chromosomal or monogenic disorders. These patients had more readmissions, longer mean stays, and a higher mortality rate than the group as a whole. In two of the four cases that died of single gene disorders, failure to store DNA made genetic counselling difficult.

In developed countries genetic disorders account for about 6% of the admissions to general paediatric wards.[1] New molecular genetic, cytogenic, and obstetric techniques offer families the prospect of avoiding recurrences of an increasing number of serious inherited conditions.

The aims of this study were to find out what proportion of the admissions to the paediatric intensive care unit were for the treatment of genetic diseases, and to audit the storage of DNA or tissues that are important for the subsquent counselling of families.

Patients and methods

The intensive care unit at this hospital is a 12 bedded unit and serves the west of Scotland, a population of roughly three million people. It combines the regional paediatric cardiothoracic unit and the general paediatric intensive care unit. Basic data including length of stay, outcome, discharge diagnosis, and any readmissions were recorded for 821 consecutive admissions to the unit between January 1987 and 31 June 1988. Each patient was assigned to one of five diagnostic categories that were described in a previous study of paediatric hospital admissions.[1] (1) Single gene, chromosomal, or mitochondrial DNA disorders. (2) Multifactorial/polygenic conditions—for example, cleft palate, asthma, most congenital heart diseases, and seizures. (3) Congenital malformations not assigned to category 2—for example, renal anomalies and multiple congenital anomaly syndromes. (4) Familial disorders not included in the above categories—for example, prematurity, malignancy, and near miss cot death. (5) Non-genetic disorders—for example, trauma and infections.

Statistical analysis was by the χ^2 test, and a probability of <0·05 was accepted as significant.

Results

Of 821 admissions to the unit during the 18 months of the survey, 14 (1·7%) could not be assigned to categories because of lack of information or follow up.

ADMISSIONS BY CATEGORY

Category 1

Forty seven admissions (6%) were due to clearly genetic disease (table 1).

Table 1 Genetic disorders for which children were admitted to the paediatric intensive care unit

	No of patients	*No of admissions*
Chromosomal:	10	13
Trisomy 21	8	
Ring chromosome 8	1	
Trisomy 18	1	
Autosomal dominant:	6	9
Malignant hyperpyrexia	1	
Velocardiofacial syndrome	1	
Holt-Oram syndrome	1	
Crouzon's disease	1	
Neurofibromatosis type 1	1	
Benign familial pemphigus	1	
Autosomal recessive:	16	21
Aminoacidaemia	2	
Mucopolysaccharidosis	2	
Metabolic encephalopathy	7	
Cystic fibrosis	2	
Idiopathic arterial calcification	1	
Congenital cataract	1	
Ataxic telangiectasia	1	
X linked:	4	4
Goltz syndrome	1	
Chronic granulomatous disease	1	
Hypergammaglobulinaemia	1	
Lowe's syndrome	1	

Category 2

There were 392 admissions (48%) for multifactorial disorders. Of these 235 (60%) were due to congenital heart disease, the remaining 157 were due to epilepsy (n=60), cleft lip and/or palate (n=29), asthma (n=26), diabetes (n=11), neural tube defects (n=9), scoliosis (n=9), hydrocephalus (n=7), and cerebral palsy (n=6).

Category 3

Thirty four children admitted (4%) had congenital anomalies; single malformations occurred in 22 (65%) and multiple abnormalities in 12 (35%).

Category 4

Eighty six children admitted (10%) had familial disorders. Of this group 31 (36%) had malignancies, 21 (24%) the sequelae of prematurity, 19 (22%) renal disorders, and 15 (17%) 'near-miss' sudden infant death syndrome.

Category 5

There were 248 admissions (30%) for non-genetic disease. Of these 149 (60%) were due to infection, the remaining 99 were due to trauma (n=31), drug ingestion (n=20), surgical abdominal emergencies (n=19), scald or burn (n=11), smoke inhalation (n=8), inhaled foreign body (n=5), non-accidental injury (n=4), and adder bite (n=1).

LENGTH OF STAY AND OUTCOME (TABLE 2)

In category 1 there was a significantly higher rate of readmission compared with category 5 (χ^2=20·6, p<0·001) and the whole group (χ^2=8·14, p<0·01), a longer mean length of stay, and a significantly higher mortality rate than both the whole group (χ^2=5·04, p<0·05) and category 5 (χ^2=7·08, p<0·01).

RISKS OF RECURRENCE AND COUNSELLING

The risks of recurrence for the families of the 36 patients (47 admissions, 11 readmissions) with category 1 diagnoses were 1·5% or less in 13 cases (10 new chromosomal abberations, three presumed new mutations of autosomal or X linked dominant genes); 25% in 19 cases (16 autosomal and three X linked recessive disorders); 50% in two cases (autosomal dominant phenotypes with a positive family history); and unknown in two cases with autosomal dominant conditions in which the parents were not examined.

Table 2 Number of patients and admissions and mortality

Category	*No of patients*	*Admissions*		*No (%) who died*	*Mean length of stay (days)*
		Total No (%)	*No (%) of readmissions*		
1	36	47 (6)	11 (23)	8 (22)	8·6
2	360	392 (48)	32 (8)	20 (6)	3·8
3	22	34 (4)	12 (35)	3 (14)	6·3
4	70	86 (11)	16 (19)	20 (29)	4·7
5	237	248 (30)	11 (4)	19 (8)	3·5
Unclassified	13	14 (2)	1 (7)	6 (46)	Not known
Total	738	821 (100)	83 (10)	76 (10)	4·2

Seventeen of the 36 category 1 families (47%) had received formal genetic counselling. Of these, four probands had conditions that can be diagnosed prenatally by established techniques. In two of these families, however, failure to store DNA or a fibroblast cell line made this impossible. The disorders in these two cases were Lowe's syndrome (oculocerebrorenal syndrome) and Hurler's syndrome (mucopolysaccharidosis type 1).

Discussion

The incidence of genetic disease in this study (5·7%) is within the range 3·5–7·1% reported in other studies of paediatric inpatients.[1 2] Half of the deaths in category 1 were of recessive conditions (two X linked, two autosomal) with risks of recurrence of 25%. The single gene and chromosomal disorders also had a higher readmission rate and longer stay in the intensive care unit. Their prevention thus assumes importance for both affected families and health care planners.

Storage of DNA or cell lines, or both, is [redacted]

best placed to provide the staff with advice about conditions that can be diagnosed and confirmed by genetic testing, and about sampling techniques and appropriate storage.

Although our study showed that single gene disorders accounted for a small but important proportion of the intensive care unit caseload, it is probably an underestimate. For example, in a recent survey of cases of Reye's syndrome, it was found that in 36% the diagnosis was revised to 'inborn errors of metabolism'.[4] Thus there are almost certainly genetic disorders awaiting delineation that will account for some cases in diagnostic categories such as sudden or 'near-miss' infant death.[5] In the light of this we recommend that all children and infants with unexplained life threatening illnesses that require intensive care should have urine, serum, and whole blood (EDTA) stored at −70°C. Careful consideration should also be given to obtaining a skin biopsy specimen for fibroblast culture, and storing samples of other tissues (such as muscle and liver) at −70°C.

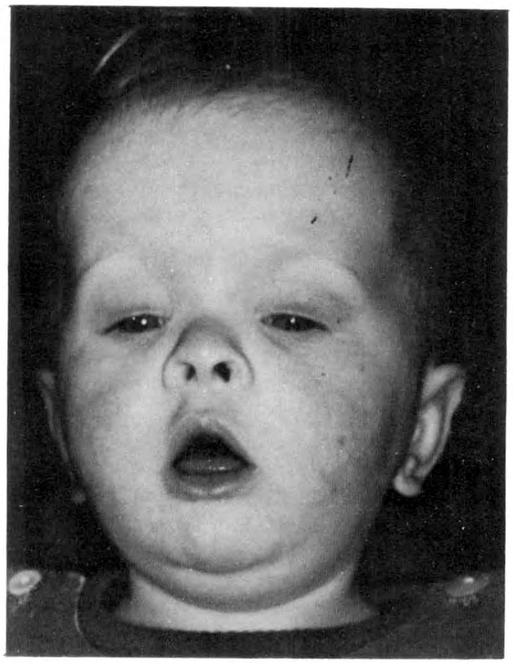


Figure 1 Frontal view of the girl aged 12 months. The forehead is broad, the nostrils are anteverted, and the nasal bridge is broad. The palpebral fissures slant downwards.

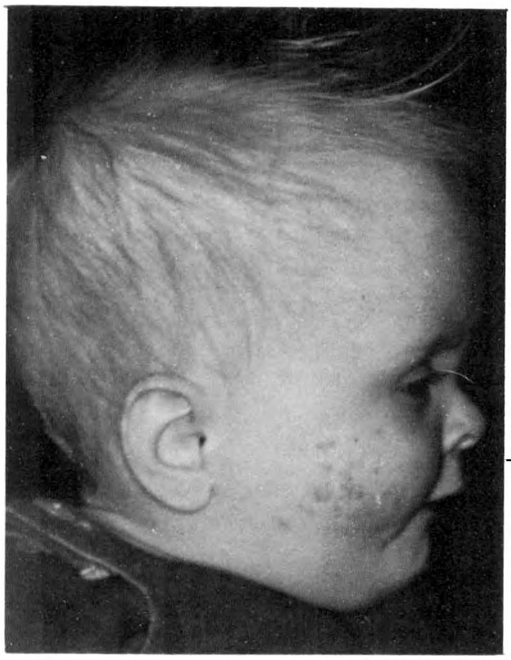


Figure 2 Lateral view of the girl aged 12 months. The forehead is prominent and the ears are set low, but not deformed. The hair is sparse, but otherwise normal.

girl was 1 week old, and no skeletal abnormalities were seen. At 14 months of age a radiograph of the hand was normal, but the bone age was only about 3 months. At 15 months, a computed tomogram of the cerebrum showed a dilated ventricular system.

At follow up at 18 months of age the girl's height and weight were below the 3rd centile, and there was generalised hypotonia and retarded psychomotor development. The dysmorphic facial appearance was still evident (figs 1 and 2). The head circumference was normal. There was no family history of malformations.

Discussion

Until now only a few children with malformations born to mothers being treated with carbamazepine alone have been reported, and descriptions of the malformations are scanty.[1–6] In a study published in 1981 the head circumferences of 20 offspring of mothers taking carbamazepine alone were on average smaller than those of a control group.[3] Among eight other infants of mothers taking carbamazepine alone a few were reported to have reduced head circumference or slight facial dysmorphism, but they were not followed up.[4]

In a multicentre investigation malformations were described in four infants born to mothers taking carbamazepine alone. These malformations were spina bifida, congenital heart disease, diaphragmatic hernia, and digital hypoplasia and hydronephrosis.[5] In another multicentre investigation a single case with a low birth weight and reduced head circumference was reported, but no details were given.[6]

In 1989 Jones *et al* reported intrauterine weight reduction and craniofacial abnormalities in a retrospective study.[2] In a prospective investigation of 35 infants of mothers taking carbamazepine alone they found that some of the children had growth retardation, facial abnormalities, developmental delay, or hypoplastic fingernails. In contrast to those of Jones *et al*[2] and Bertollini *et al*[5] our case did not have hypoplastic finger nails. In four of 35 cases Jones *et al* found palpebral fissures that slanted upwards. In contrast, our case had palpebral fissures that slanted downwards.

Carbamazepine seems to be associated with different patterns of defects.[2] In our case we found intrauterine growth retardation and a dysmorphic facial appearance. At follow up at 18 months of age growth retardation and mental retardation was evident. In the study by Jones *et al* developmental delay was found in 20% of the children who underwent formal neurobehavioural assessments.[2] Until now only a few reports have been published describing malformations in children born to mothers taking carbamazepine alone. This may be because carbamazepine is only slightly teratogenic, or because the problem is unrecognised. The published reports together with our case seem to indicate that carbamazepine alone may have a teratogenic effect, but a possible phenotype of carbamazepine teratogenicity has not yet been identified.

1 Kaneko S, Otani K, Fukushima Y, *et al*. Teratogenicity of antiepileptic drugs: analysis of possible risk factors. *Epilepsia* 1988;**29**:459–67.

2 Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 1989;**320**:1661–6.

3 Hiilesmaa VK, Termao K, Granström ML, Bardy AH. Fetal head growth retardation associated with maternal antiepileptic drugs. *Lancet* 1981;**ii**:165–7.

4 Kuhnz W, Jäger-Roman E, Rating D, *et al*. Carbamazepine and carbamazepine-10,11-epoxide during pregnancy and postnatal period in epileptic mothers and their nursed infants: pharmacokinetics and clinical effects. *Pediatric Pharmacology* 1983;3:199–208.

5 Bertollini R, Mastroiacovo P, Segni G. Maternal epilepsy and birth defects: a case-control study in the Italian multicentric registry of birth defects (IPIMC). *Eur J Epidemiol* 1985;**1**:67–72.

6 Bertollini R, Kallen B, Mastroiacovo P, Robert E. Anticonvulsant drugs in monotherapy. Effect on the fetus. *Eur J Epidemiol* 1987;**3**:164–71.

Providing medical care for children

David Hull, *President of the British Paediatric Association*

This is the second in our series of papers showing the problems facing the medical services for children in different countries.

That 'enterprise' which brings the benefits of medical science to the British, the National Health Service (NHS), is undergoing a managerial reorganisation. The overall objectives of the 'health service industry' are stated in the white paper. Good management requires that there is something in it for those who own the 'factory' and something for the 'workers'. The owners also happen to be the customers, such is the nature of nationalised industries. For them the aim is to provide better health care and greater choice of the services. For the staff there is to be greater satisfaction and rewards for those working in the NHS who successfully respond to local needs and preferences. No one can take exception to either of these ambitions.

The NHS is not a manufacturing industry but a service. We do not have a product like a can of beans, we provide a service, the item of service is the interaction between the patient and a health professional. The problem with the current arrangement in the NHS is that those who 'lay on hands' aim to do the best for their patient and acknowledge no financial restraint, indeed they have little influence over those who allocate resources. Currently those who control the resources are unable to allocate them in a way that acknowledges the medical needs, however those are defined, of the people they serve. Health authorities, the purchasers, who buy the service on behalf of all of us, are required to ensure that (1) there are effective services for the prevention and control of diseases and the promotion of health, (2) their population has access to a comprehensive range of high quality, value for money services, and (3) they set targets for and monitor the units for which they continue to have responsibility.

In Nottingham those of us working with children have interpreted these notions with respect to the service we provide for children to give us the following objectives:

- To provide a quality service to all children when and where it is most appropriate
- To support families in the care of their children
- To take whatever actions we can to ensure that as many children as possible reach adulthood with their potential uncompromised by illness or environmental hazard
- To provide a single comprehensive service
- To introduce audit in the framework of quality management.

We have tried to spell out the implications of these objectives in our service statement.

It is inevitable that as we try to understand the new management arrangements and how they will affect the service we hope to provide for children, that we will get entangled with the details and we will be frustrated and perhaps disappointed by the frameworks that are applied to control our own working practices. Notions like 'smooth take off', 'level transfer', 'letters of comfort', 'mission statements' have at least a certain 'Alice in Wonderland' charm. But we must not make the mistake that Alice did when she asked the Cheshire cat which way she should go. If we have no vision of what we want for the medical services for children then we must not complain about the way we are managed. How can the 'managers' know if we do not tell them.

1991 provides us with an excellent opportunity to consider what we would want, what changes we would like to see, and what problems we would like addressed. The situation requires that we are realistic and reasonable, this is not the time to dream of what might be if we lived in a community which shares our values or a UK with a flourishing economy and a world without war and famine. It does mean however that we need not bind ourselves to arrangements which have been hallowed by time. It is not self evident, as many of the proposed arrangements appear to envisage, that hospitals working on outpatient and inpatient activities are the best way to provide the service.

The 'balanced district general hospital', that egalitarian dream of the last reorganisation which resulted in the closure of many small children's hospitals, left those of us concerned with children repeatedly stating that children are different and need special consideration not because they suffer from *strange childhood illnesses* but because they are *children*.

We might be forgiven, but then again we might not, if we again state the obvious. Yes children are a burden, no they do not produce, yes they need care and protection whether they are ill or not, *but* they are the sowers and the gatherers of the future. They need a medical provision which is tailored to their special needs, it is nonsense to adapt services designed for adults by an adjustment in time or scale, that is usually as dangerous and misguided as reducing the height on 20% of the steps on the stairs in the hospital because 20% of those who use the stairs are children who have shorter legs.

The argument for giving the medical services for children the highest priority rests not on the emotional appeal of 'women and children first' but on the grounds that a healthy future generation is the best way of looking after the wellbeing of us all. Put in negative and harsh terms, a damaged child becomes a damaged adult and for the 'Medical Industries Inc' they are a long

Correspondence to:
Professor David Hull,
Department of Child Health,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH.

and expensive non-economic drain on resources. This is well illustrated by the size of the 'one off' pay settlements awarded by judges when doctors have been found at fault in the care they provided for a child who is left damaged. In such matters judges do not recognise the welfare state! What I propose in this brief statement is to highlight some of the challenges inherent in the proposed changes.

Specialist, high tech care

Here we must face some painful choices. We should not complain too much for in most of the world they do not even have the choice. What should be the 'outcome measures' against which we audit our expensive high tech medical services like intensive neonatal care, cardiac surgery, neurosurgery, oncology services, etc? The outcome measures which are most easily measured are mortality rates. For example perinatal mortality has been a popular measure of health service provision in the past, the first UK Perinatal Mortality Survey had a major impact on the future provision of services: women went to hospital to have their babies, and each maternity unit has a neonatal unit.

And yet it has not been a primary objective in Nottingham for us to reduce our perinatal mortality rate for some 10 years, though obviously we would like it to be nothing (or at least better than anyone elses!). Of more concern to us is the handicap rate. Given the current technology for the care of infants on the edge of viability we often achieve survival with the near certainty of handicap. It is an unhappy fact that doctors who specialise in neonatal medicine rarely have to face up to the consequences of their 'success'. The legal position is no protection, the law by its very nature follows events, here whether we like it or not we have to decide what is good and what is bad. But the moral debate is no easier, destruction in utero four weeks earlier in gestation is desired by many families if the fetus is abnormal. We provide a service to our customers, is the customer always right? Can we find refuge in the thought that it is what we would want for our own child. What would you want if your child, born at 24 weeks' gestation, was ventilator dependent on day 7 with grade 4 intraventricular haemorrhage? If you controlled the budget would you invest more and more in the sophisticated tools of neonatal intensive care when there is good evidence that gentleness and minimal intervention causes less damage? It might be difficult to establish one way or the other whether taking control by active interventions or by judicious but selective support leads to the lower neonatal mortality rate. Doing and trying always seems the more commendable approach.

The time has come when we have to make some difficult choices. The control of services for the special and intensive care of newborn infants must stay close to the people who are served, the purchasers must know about the people, their concerns, their hopes and their dreams, and they must learn what happens to the fragile creatures that are handed to their parents when they leave such units. It is wrong to give parents a responsibility they, with the best will in the world, cannot carry. We must not be surprised to be told yet again that premature birth and low birth weight are good indices of disadvantage, nor should we pretend that it is not so. Ordinary folk in distress or passing through troubled times have different priorities to the noble well resourced.

So the future of intensive neonatal care needs to be examined carefully. Small units are unlikely to do it well, technically or economically. Regional health authorities have shed their responsibility for intensive neonatal care, they appear to have left it to 'market forces' to establish new networks. It seems to me that all maternity units need level 1 and 2 neonatal services, and that *they* should control the transfer to and from a level 3 centre whose quality management, system, control and assessment, are public knowledge and subject to external audit from the beginning. The UK has too small a population and our resources are too limited to allow everyone who wishes to do level 3 care to do it. It should no longer be the stalking territory of the enthusiastic neonatologist.

Debate along similar lines could be followed for most of the specialist tertiary services for children, as well as for the intensive care of older children.

Family care

Once infants leave the hospital in which they have been born their care is the responsibility of their parents. Initially parents may need support and help in their new task, and this is the time when any support is most welcome and is likely to be most effective. Help with early rearing was one of the main reasons why health visitors were appointed and the child health service (infant welfare clinics) were established. Very quickly the parents become the experts in the care of their child. Infants are very dependent on their parents' awareness and skill in attending to their needs. When an infant falls sick, those skills become especially important, the art of caring for sick children is to make optimal use of this awareness and skill for the child's benefit. Again this is not just a soft cuddly notion about the sanctity of the family, or an example of parents' 'rights'. Examination of hospital statistics shows that the majority of children admitted to hospital with medical conditions are under 2 years of age, they have acute illness requiring emergency admissions, and that they are in hospital for one or two days only, Given that scenario, it is unthinkable, if we aim to provide a quality service, not to have adequate and acceptable accommodation for the child's parents, and not to accept that it is the primary duty of the staff to support the parents in the care of their child. In Nottingham we explored the concept of 'parent care units' and concluded that it was inappropriate for our service, parent care is not an extra for some children, nor an economic option, it is central to the care of all children. We are, of course, aware that it is sometimes the parents who need the care, we only wish we were able to address that need more directly. Our primary responsibility is to the child, it has taken longer than could possibly have been imagined to persuade hospital management that parents staying in hospital need resources. Any contract for hospital services for children should include a clear statement of what is provided for parents to assist them in continuing their vital contribution to the care of their sick child.

The problem with the introduction of change is that managers and staff alike retreat into well tried (but not necessarily effective) arrangements understood by everyone. The government, and those who drafted the white papers on the Health Services Act are no exception. They speak of hospital trusts. It is not unexpected to find that those seeking such status are hospitals. No one doubts that hospitals are fine institutions in which to receive surgical attention. It does not follow that it is also the optimal environment to recover from surgery or be cared for when one falls ill with disease not open to surgical remedy. Over the last few years in paediatric medicine there have been many successful attempts to transfer the 'hospital care' of children, particularly those with chronic illness, from the hospital to the home and school. Thus services have been developed to support the family in the home and the teachers in the school. It would be a retrograde step to insist that this work takes the form of 'outpatient' or 'inpatient' activity so that the staff duties are accountable. For example, consultant 'fixed sessions' do not make much sense for a doctor who provides a service for families with a diabetic child, any more than they do for an inpatient service with an average length of stay of two days.

Health care

The medical services for the newborn are the entry point into the medical services for children, they are the point of first contact. In one sense they are a primary care service. In the UK we have a fine tradition of general practice. The proposed new arrangements are important because they introduce health promotion activities formally into family practice. How these will work out in the inner city areas where they are perhaps most needed remains to be seen. They may also bring with them 'duties' which are difficult to foresee: if a child is not vaccinated, is the family doctor liable? Has he failed in his responsibilities to the child. The World Health Organisation holds the view that no child should be denied the protection that an immunisation programme can give, and this is echoed in Department of Health advice. Doctors are being sued because they recommended against the pertussis vaccine and the child was subsequently damaged by the illness.

It would be as wrong in this matter, as it is in other areas, to run for cover just because the 'rules' are a little confused. We must do what we believe to be best for the child. In this matter as in the care of their children when they are ill, parents have the major responsibility. They will want to know what they can do to look after their child's interests. A major advance is the introduction of a parent held record. There can be no doubt that this will increase in sophistication in the future. If I can go to cash dispensers in many towns and cities of the UK and find out how much I have in my account then it should not be long before we can set up a system that ensures all the children in our area of responsibility have had the necessary health checks and immunisations. Nor should it be difficult to introduce technology which gives parents access to information, in a form that they can understand, to assist them to make the necessary decisions about the health of their child. This will inevitably change the nature of the medical interview. The doctor's task will be as it has always been, to help his or her patient to make best use of what services are available.

Shared care

The newborn child becomes a separate individual with a 'right' to life. Talking about children's 'rights' always leads to problems, and there has been a lot of talking recently. However, it need not be made too complicated. Children need care and protection and it is the parents' responsibility to provide it. This is clearly stated in the Children Act 1991. Children also need to be respected for what they are and what they understand. Due regard must be given to any wishes or opinions that they have. It is awareness and understanding of these that is the special skill of those who work with children. There is however another aspect to all this which enlarges the duties of all professionals who work with children. It relates not to their professional skills but to the fact that they are responsible adults who are aware of a child's needs. The Children Act states that a child shall be taken to be in need if (a) he is unlikely to achieve or maintain . . . a reasonable standard of health or development without the provision for him of services by a local authority, (b) his health or development is likely to be significantly impaired . . . without such services, and (c) he is disabled.

A child is in need if his or her parents are not able to provide adequate care and protection. We too have a duty to do something if we have reason to believe that the parents are not able or willing to meet the needs of their child. In a later section the Children Act defines 'harm' as ill treatment or the impairment of health or development, which is not unlike the definition of need but the implications for those who become aware that the child is 'at risk' of harm are more prescribed. The Children Act was drafted by persons of great vision, no doubt the cynics will find their way through it, but we must not let them distract us. Children when they have need or are being harmed are often brought for medical attention. Thus our responsibilities extend well beyond the exercise of our craft. The medical services for children are a social agency and must work with the other agencies if we are to meet our wider responsibilities. Much has been said and written about interagency working. I suspect we would need far less if we could all remember that our purpose is to help the child and not to overstate our own contribution or protect ourselves and our agencies from criticism.

Many of the outcome measures of the medical services for children are shared by the other agencies working with children, the law, police, social service and education, as well as many voluntary bodies. There is too much to be done for us to spend time competing or worse, squabbling.

In 1976, the Court report *Fit for the Future* set a vision for the future; perhaps its greatest contribution was to stress the importance of community services. In the 1990s we must aim to provide a single comprehensive service for children which integrates medical care with health promotion and which does not allow management boundaries or professional self interest to diminish its effectiveness.

In this brief comment on the state of the medical service for children in the UK, I have tried to state the vision, and touched on some of the implications with examples from the primary, secondary, and tertiary services. We live in interesting times, they are the only ones we have, and it will be interesting to see what we can make of them.

Archives of Disease in Childhood 1991; **66**: 647–652

PERSONAL PRACTICE

Supraventricular tachycardia: diagnosis and current acute management

Janice A Till, Elliot A Shinebourne

There is a small but potentially avoidable incidence of death associated with childhood supraventricular tachycardia.[1 2] The time of greatest risk is when the child presents for the first time and requires therapeutic intervention. Infants and children tolerate arrhythmias less well than adults as they are more dependent on heart rate for cardiac output and have less reserve.[3 4] They are also at risk from drugs given as treatment.[5] We discuss our current acute management of supraventricular tachycardia.

Diagnosis

Between 30 and 40% of children who present with supraventricular tachycardia do so within the first few weeks of life. Their presentation is variable. Supraventricular tachycardia can be the cause of unexplained hydrops of the fetus or can result in sudden profound cardiovascular collapse in the newborn period.[6] More usually neonates and small infants will present with symptoms of increasing tachypnoea, poor feeding, and pallor which have developed over a few days. Occasionally supraventricular tachycardia is intermittent and a strong index of suspicion must be maintained if the diagnosis is not to be missed. The older child more usually presents with a history of palpitations.

The most common type of supraventricular tachycardia in childhood results from a re-entry circuit between atria and ventricles involving the atrioventricular node as the antegrade limb and an accessory connection between ventricle and atrium as the retrograde limb (fig 1). This type of tachycardia, atrioventricular re-entry tachycardia, can be classified as a junctional supraventricular tachycardia (table). An accessory connection may occur anywhere around the atrioventricular ring. If it is capable of supporting conduction antegradely from atrium to ventricle, as well as retrogradely, the usual situation during supraventricular tachycardia, it will be manifest on the electrocardiogram during sinus rhythm as a short PR interval and delta wave. Such pre-excitation of the ventricle together with supraventricular tachycardia is the syndrome described by Wolff, Parkinson, and White.[7] If conduction is restricted to the retrograde direction, atrioventricular re-entry tachycardia is possible but there will be no evidence of the connection on the electrocardiogram during sinus rhythm, a situation termed concealed pre-excitation.

The majority of children with an accessory

Department of Paediatrics,
Royal Brompton and National Heart Hospital and National Heart and Lung Institute,
Fulham Road,
London SW3 6HP
Janice A Till
Elliot A Shinebourne

Correspondence to:
Dr Till.

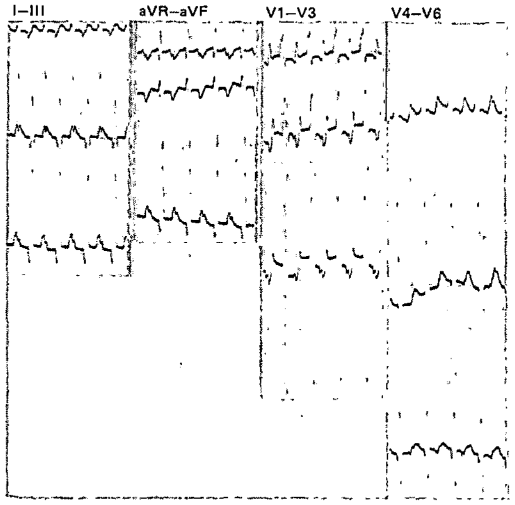


Figure 1 An electrocardiogram recorded from a 1 week old neonate with atrioventricular re-entry tachycardia showing the typical pattern with a P' wave almost midway between QRS complexes.

Classification of supraventricular tachycardia

Junctional tachycardias
Atrioventricular re-entry tachycardia (AVRT)
Orthodromic AVRT:
  Tachycardia involving a circuit utilising the atrioventricular node as the antegrade limb and an accessory connection between ventricle and atrium as the retrograde limb
Antidromic AVRT:
  Tachycardia involving a circuit utilising an accessory connection as the antegrade limb and the atrioventricular node as the retrograde limb
Atrioventricular nodal re-entry tachycardia (AVNRT)
Tachycardia involving a circuit the two limbs of which are intimately associated with the atrioventricular node. The atria and ventricles are activated as offshoots of the circuit. The common type of AVNRT is typified by slow conduction antegradely and fast conduction retrogradely, the uncommon type by fast conduction antegradely and slow conduction retrogradely
Long R–P' tachycardia
Tachycardia involving a circuit utilising the atrioventricular node as the antegrade limb and a slow conducting pathway as the retrograde limb. The latter may be an accessory connection in close association with the atrioventricular node, in the posteroseptal position or remote from the atrioventricular node
Atrial tachycardias
Atrial tachycardia
Tachycardia characterised by discrete atrial activity on the surface electrocardiogram with varying ventricular response resulting either from a micro re-entry circuit or ectopic focus confined within the atria
Atrial flutter
Tachycardia characterised by a sawtooth undulation of the baseline on the surface electrocardiogram probably resulting from conduction around a re-entry circuit within the atria
Atrial fibrillation
Tachycardia characterised by chaotic low voltage 'fibrillatory' waves on the surface electrocardiogram with an irregularly irregular ventricular response, resulting from disordered atrial actvity

connection do not have structural congenital heart disease. When there is a structural anomaly this is most commonly Ebstein's anomaly of the tricuspid valve or less frequently, corrected transposition (discordant atrioventricular connection, discordant ventriculoarterial connection).

Atrioventricular re-entry tachycardia accounts for the great majority of supraventricular tachycardias presenting in the first year of life. The spectrum of supraventricular tachycardia in older children is wider and both atrial and other junctional tachycardias such as atrioventricular nodal re-entry tachycardia or long R-P' tachycardia are more frequently seen. They can usually be distinguished from the surface electrocardiogram. Junctional tachycardias are characterised by a narrow regular QRS complex and a one to one relationship between the P' waves and the QRS complexes during tachycardia. In atrioventricular re-entry tachycardia this one to one relationship is a necessity if the tachycardia is to continue, as disruption of the relationship between atrium and ventricle will interrupt the circuit and stop the tachycardia. Typically during atrioventricular re-entry tachycardia there is a P' wave easily seen following the QRS complex. This is because the atria are depolarised only after the electrical impulse has travelled sequentially through the His-Purkinje system, ventricular muscle, and accessory connection. There is therefore a time interval, usually greater than 70 msec, between ventricular and atrial depolarisation. In contrast, during atrioventricular nodal re-entry tachycardia the atria and ventricles are both activated as offshoots of a re-entry circuit involving a fast and slow pathway in close association with the atrioventricular node. The retrograde pathway is typically fast and therefore atria and ventricles are depolarised almost simultaneously. As a result the P' wave is not easily seen, being hidden from view by the QRS complex. The other less common junctional tachycardia, the long R-P' tachycardia, can often be distinguished by its 'persistent' nature, stopping and starting during the electrocardiogram recording, and the characteristic superior P' wave axis, seen just before the QRS complex (fig 2). This electrocardiographic pattern represents a re-entry circuit involving the atrioventricular node antegradely and a slow conducting pathway, which may either be an accessory pathway or part of the atrioventricular node, retrogradely. It is this long interval between the R wave of the QRS complex and the P' wave, representing slow conduction in the retrograde pathway, that gives the tachycardia its name.[8]

Atrial arrhythmias, for example, atrial tachycardia, atrial fibrillation, or flutter, are not often seen in the first year of life. They are more common, especially after cardiac surgery, in the older child with structural heart disease where the atria are distorted or distended, or in the child with myocarditis. They may occasionally be seen in association with an accessory connection. Unlike the more common junctional tachycardias they can continue in the presence of atrioventricular nodal block; a one to one relationship of atrial to ventricular depolarisation is not required.

Before any treatment is administered the tachycardia should be documented by recording a 12 lead electrocardiogram and rhythm strip. This is important as correct diagnosis of the arrhythmia should guide treatment and prevent use of inappropriate or potentially hazardous drugs. Ventricular tachycardia should be excluded. Ventricular arrhythmias are relatively uncommon in childhood. When they do occur

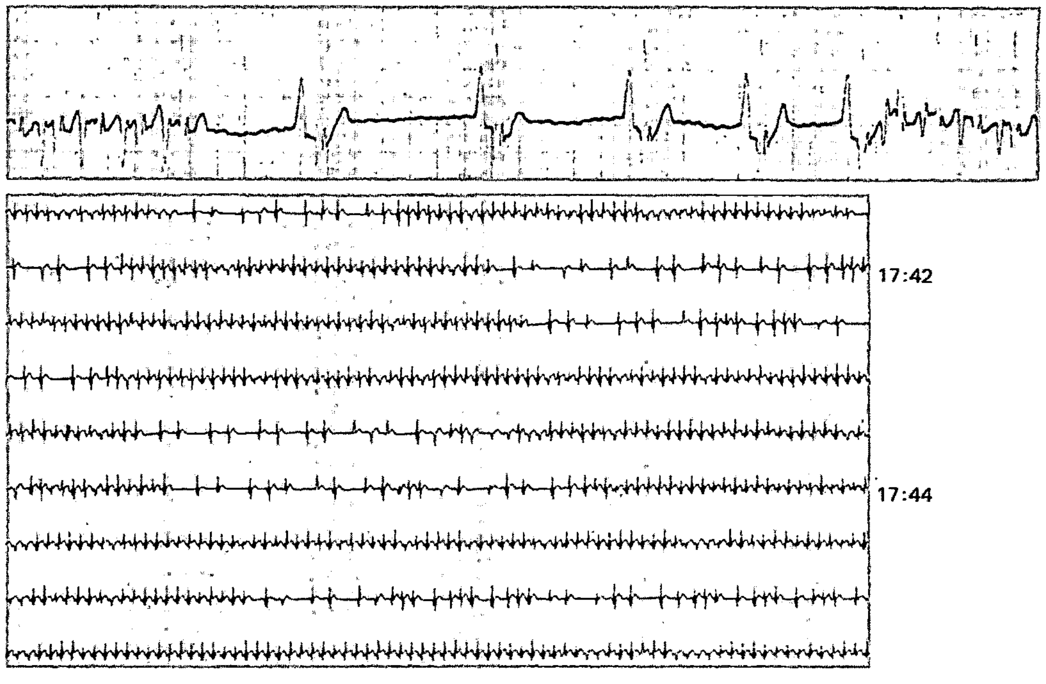


Figure 2 A section from a 24 hour tape recording performed on an infant with a long R–P' tachycardia. The electrocardiogram (top) (25 mm/sec), shows the tachycardia with P' wave (inverted) just before the QRS complex, terminating spontaneously. There follows four beats of sinus rhythm before the tachycardia reinitiates. The three minute sequence shown below shows how this behaviour continues repeatedly.

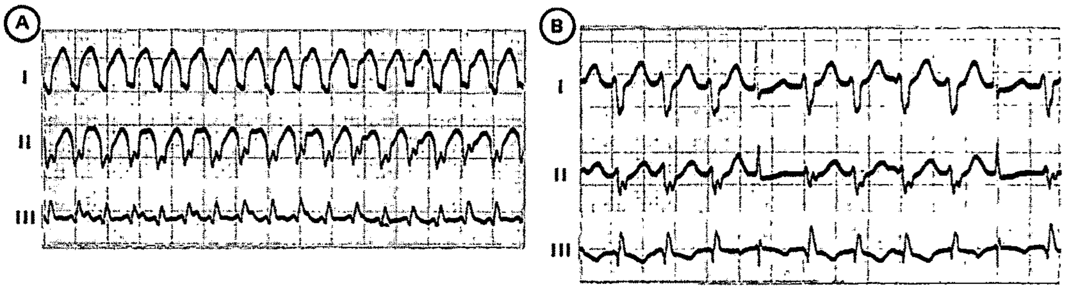


Figure 3 (A) Leads I, II, and III from an electrocardiogram recorded from a 1 year old child with ventricular tachycardia. The child had an otherwise structurally normal heart, no electrolyte inbalance, and was haemodynamically stable at the time of the recording. The rate is 320 bpm and atrioventricular dissociation can be seen. (B) Similar leads taken from an electrocardiogram recorded from the same child some hours later after a spontaneous slowing of ventricular tachycardia rate. Capture beats are now seen (4th and 9th QRS complex).

they are most frequently only recognised after a cardiac arrest as a result of inappropriate drug treatment given in the mistaken belief that the arrhythmia being treated was supraventricular tachycardia.[5] Unfortunately the electrocardiographic appearances of ventricular tachycardia are not typical in early life. The QRS complex is not neccessarily grossly widened and the rate may exceed 300 beats/minute (bpm). Helpful signs are an abnormal QRS axis for age, the presence of fusion or capture beats and atrioventricular dissociation (fig 3). It is rare for supraventricular tachycardia to have a wide QRS complex in childhood but may be seen in association with Ebstein's anomaly,[2] after cardiac surgery requiring a ventriculotomy or after treatment with antiarrhythmic drugs. Then the morphology of the QRS complex closely resembles that of either right or left bundle branch block (more commonly right). Comparison with previous electrocardiograms, if available, is invaluable as the presence of bundle branch block most often predates the onset of tachycardia. It is comparatively rare to develop bundle branch block as a result of tachycardia.

Treatment

The ideal acute management of supraventricular tachycardia is a subject hotly debated by cardiologists, but in practice, one that depends on facilities locally available. If the child is tolerating the arrhythmia well and the supraventricular tachycardia is judged to be one of the more common junctional tachycardias, atrioventricular re-entry tachycardia or atrioventricular nodal re-entry tachycardia, there are a number of options available, any of which are acceptable. Our current recommendations are outlined in fig 4.

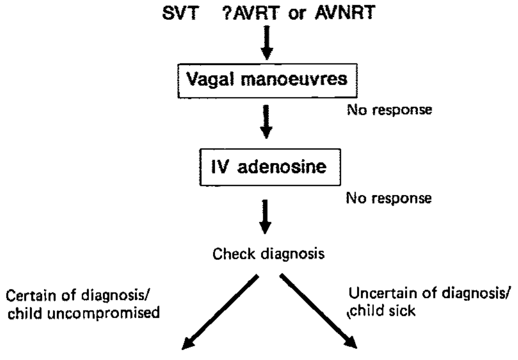


Figure 4 Acute management of supraventricular tachycardia (SVT) in childhood: current recommendations. AVRT, atrioventricular re-entry tachycardia; AVNRT, atrioventricular nodal re-entry tachycardia.

Vagal manoeuvres are easy to perform, quick, safe, and often successful.[9] Immersion of an infant's face in cold water, to elicit the diving reflex, appears to be very effective.[10] Some older children will actively participate in vagal manoeuvres, particularly if it is not their first attack. Others are too frightened and attempts at immersing their face in cold water do little to improve this. If vagal manoeuvres fail drug treatment may be considered.

Digoxin has been used to treat supraventricular tachycardia for many years. It has advantages in that it is familiar and is not negatively inotropic. More recently digoxin has fallen from favour because of the danger of inappropriate treatment of ventricular tachycardia, where it may precipitate ventricular fibrillation, and because of the slowness of its action (median time six hours).[11] In preference therefore we would chose adenosine as the drug of first choice for the treatment of acute supraventricular tachycardia. Adenosine is a new drug with many attractive characteristics. It acts by slowing atrioventricular nodal conduction thus disrupting a re-entry circuit (fig 5). It has a rapid onset of action and is effective within 10 to 20 seconds of being given intravenously in approximately 86% of junctional tachycardias.[12–14] It has a short half life of 10–15 seconds so side effects, which occur in one third of patients treated, are transient and rarely require intervention. Additionally adenosine is not negatively inotropic in this form and so may be given to an infant or child in low cardiac output without fear of exacerbating this. Moreover if adenosine is administered to a child with ventricular tachycardia by mistake it will not precipitate ventricular fibrillation. Indeed a bolus of adenosine can be used in the difficult situation of a wide complex tachycardia as a diagnostic aid to help distinguish ventricular from supraventricular tachycardia.[15] The main disadvantage of using adenosine is that in approximately 30% of cases the tachycardia will reinitiate. None the less because of its high safety profile it is our drug of first choice.

Verapamil is highly effective in terminating supraventricular tachycardia in children as in adults and has been advocated in the past as the treatment of choice for the acute management of supraventricular tachycardia.[16–18] Verapamil has the advantage that it brings about termination of tachycardia in a more gradual fashion than adenosine and the tachycardia is less likely to reinitiate soon after stopping. Verapamil is negatively inotropic, however, and suppresses both sinus and atrioventricular node function and within the last few years reports have been published of infants reacting to verapamil with profound bradycardia and hypotension.[19–21] In some cases this has been irreversible despite the use of calcium. Deaths such as these have caused physicians to suggest that verapamil should never be used in infancy. Undoubtedly some of the reported cases have been due to inappropriate use, such as following the administration of β blockers or in infants with known severe ventricular dysfunction,[5] but there is some evidence to support the notion that young infants are more sensitive to verapamil than adults.[22] As there appears to be a safe alternative in the form of adenosine we have adopted the latter drug when treating infants less than 1 year of age.

Flecainide is a further antiarrhythmic drug which may soon be licensed for use in children in this country. Like other class 1c drugs it has a different mode of action from the drugs so far discussed, exerting profound effects on the accessory connection as well as the atrioventricular node. Typically when used to terminate supraventricular tachycardia, the arrhythmia will be seen to terminate with a QRS complex as retrograde conduction in the accessory connection is prevented (fig 5). It is useful, therefore, in the management of those tachycardias that are refractory to vagal manoeuvres or adenosine.[23] It also has actions on the atria and can be used to treat atrial arrhythmias.[24] However flecainide is negatively inotropic and can be proarrhythmic. It should therefore be given slowly over at least 10 minutes with careful attention to the electrocardiogram and blood pressure.

Other therapeutic options available when dealing with the acute situation are direct current (DC) cardioversion or pacing, either via an oesophageal or transvenous electrode. If the child is sick and a rapid response with no further depressant effect on cardiac output is required vagal manoeuvres can still be tried. Intravenous adenosine is safe and effective, if readily available (see footnote), but if not, DC cardioversion should be tried. We use one joule/kg in the first instance. If the QRS complex is wide but supraventricular tachycardia is suspected, vagal manoeuvres or intravenous adenosine can still be safely given. Because of the risk that a wide QRS complex tachycardia may be ventricular in origin verapamil and digoxin should *not* be used. Pacing techniques can be very effective and are relatively easy to apply,[25 26] but equipment is usually available only in cardiac centres.

Of the many other antiarrhythmic drug available all have potential disadvantages. In the acute situation when vagal manoeuvres and adenosine have failed we use flecainide if ventricular function is not seriously impaired. If ventricular function is impaired we would try DC cardioversion or pacing to prevent further deterioration. We chose flecainide because it is a

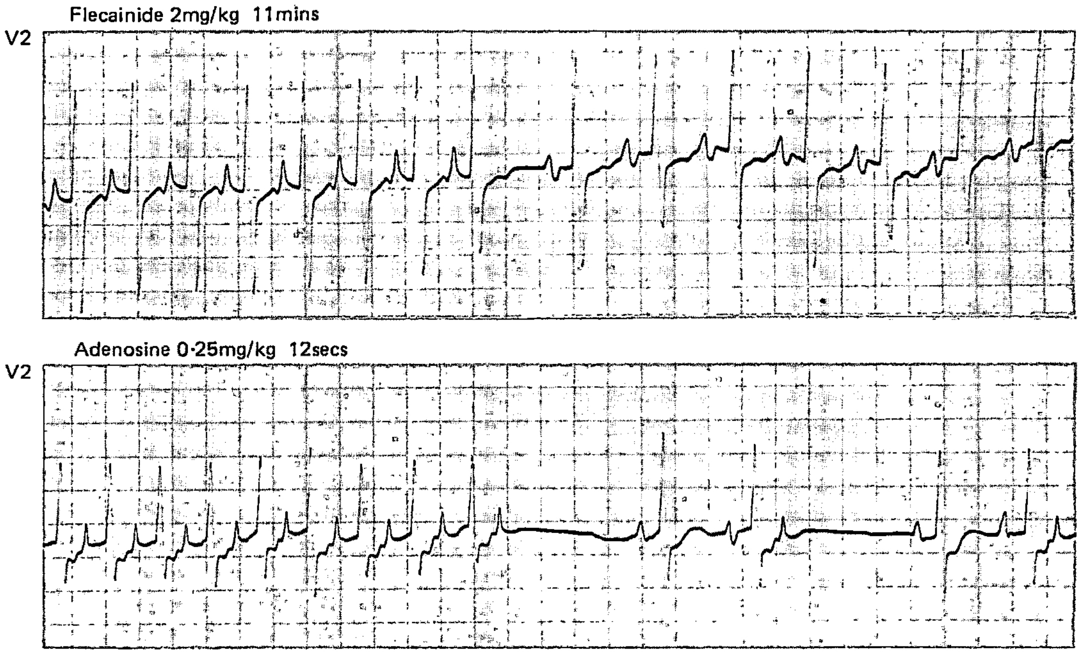


Figure 5 Two rhythm strips of lead V2 recorded from a child with atrioventricular re-entry tachycardia. The upper strip is recorded after the administration of intravenous flecainide showing the typical response of a slowing tachycardia rate followed by termination. Termination characteristically occurs in the limb of the circuit formed by the accessory connection (the tachycardia stops after a QRS complex). The lower strip is a recording from the same child on a different occasion after the administration of intravenous adenosine. The tachycardia terminates in the atrioventricular nodal limb of the circuit (the tachycardia stops after a P' wave), a sinus beat follows, and then the next sinus beat is followed by an atrial echo beat. This pattern continues until sinus rhythm resumes.

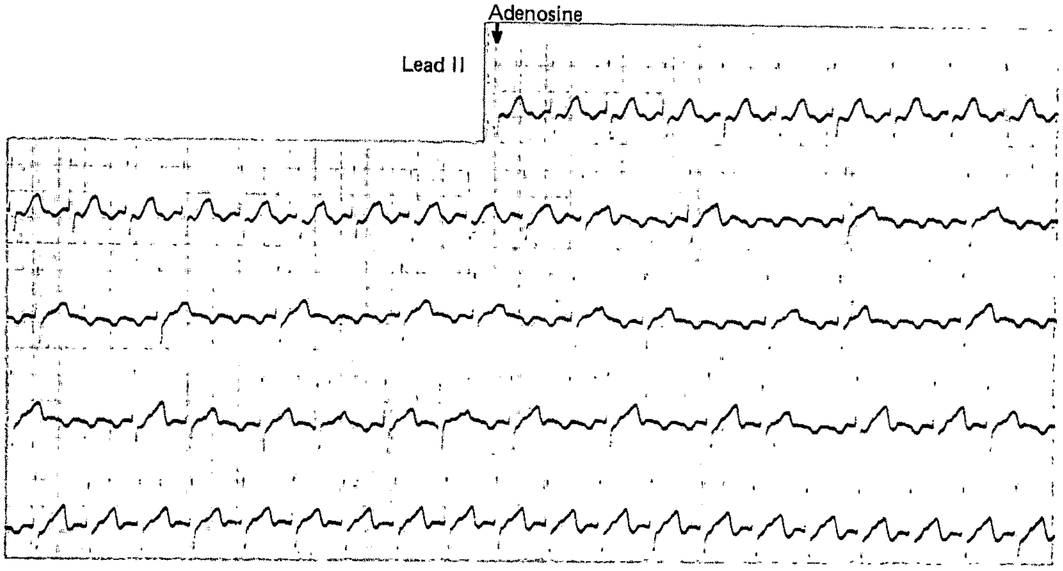


Figure 6 Electrocardiogram recorded from a child with atrial flutter showing the typical response of atrial flutter to intravenous adenosine. Adenosine fails to stabilise the atria but causes a transient slowing of ventricular rate as a result of an increased degree of atrioventricular nodal block, allowing confirmation of the diagnosis.

class 1 drug with with which we are familiar. Preliminary studies in children using propafenone are also favourable.

Atrial arrhythmias, in contrast to junctional, seldom respond to vagal manoeuvres and atrioventricular nodal blocking drugs such as adenosine or digoxin merely slow the ventricular rate rather than stopping the tachycardia (fig 6). DC cardioversion may be more effective at restoring sinus rhythm in this situation. Otherwise a class 1 drug such as flecainide may be necessary to stabilise the atria. If digoxin is used in an attempt to slow the ventricular rate, underlying Wolff-Parkinson-White syndrome must be excluded first, as digoxin may allow an increase in the conduction of atrial impulses to the ventricle via the accessory connection thus precipitating ventricular flutter or fibrillation.[27 28]

For those children with structural congenital heart disease particularly those who develop arrhythmias late after surgery management is less easy. Surgery may leave a child with ventricular dysfunction and arrhythmias may be poorly tolerated requiring prompt treatment. Negatively inotropic drugs must be used with great care in this group for fear of exacerbating ventricular dysfunction.[29] Trauma to the sinuatrial junction at the time of operation may result in sinus node dysfunction and conversion from a rapid tachycardia may disclose an inadequate recovery response from the sinus node. Children who have undergone the Mustard or Senning procedure for transposition of the great arteries, or those who have survived the Fontan procedure most commonly used for tricuspid atresia or double inlet left ventricle, are frequent sufferers of recurrent atrial arrhythmias, often in the setting of sinus node dysfunction, so called tachybrady syndrome.[30 31] Such children present very difficult management problems and conversion from tachycardia should ideally only be attempted if facilities are available for temporary pacing.

Prognosis

After the diagnosis and successful termination of the first attack the prognosis for children with atrioventricular re-entry tachycardia presenting in the first month of life and early infancy is good and many have no further attacks.[1 2] However, we frequently chose to treat all children for the first year of their lives. After this, they are better able to communicate their problem and are less likely to become haemodynamically compromised should they develop further episodes of supraventricular tachycardia. The cause of the apparent resolution of the condition is unclear. Some authors have suggested that the accessory pathway in such children disappears completely as if the heart were completing its developmental process after birth. Other authors have suggested that the accessory pathway merely becomes dormant and have shown that the triggers required to initiate the re-entry circuit change with increasing age.[32 33]

In terms of freedom from recurrences of arrhythmias the long term prognosis for children presenting later in their lives is not as good as in those infants presenting with the first year as they are less likely to 'grow out' of their tachycardias.[2] Even children with atrioventricular re-entry tachycardia and an otherwise structurally normal heart, presenting at this age, tend to continue having attacks of supraventricular tachycardia; their accessory connection persists. The majority can still be controlled with the commonly available antiarrhythmic agents and in this country drug treatment remains the mainstay of treatment, although we recognise that surgical interruption or ablation of arrhythmogenic substrates such as accessory pathways is successful even in the very young.[34 35] The high success rate and low morbidity now achieved with surgery make this an increasingly appealing option, offering these children a potential cure rather than life long palliation. Arrhythmias in children with structural heart disease remain a difficult problem. Treatment in this group remains far from ideal and arrhythmias continue to threaten the lives of such children.

An increased interest in arrhythmias in the young and the advent of electrophysiological studies in children has allowed a better understanding of the mechanisms underlying childhood supraventricular tachycardia. This in turn has paved the way for a more logical approach to treatment. With careful attention to the electrocardiogram and a working knowledge of the therapeutic options available, deaths during this hazardous initial period can hopefully be avoided.

Adenosine does not yet have a product license but is available in the United Kingdom. For further information please contact the pharmacy, Royal Brompton and National Heart Hospital.

1 Giardina ACV, Ehlers KH, Engle MA. Wolff-Parkinson-White syndrome in infants and children. A long-term follow-up study. *Br Heart J* 1972;**34**:839–46.
2 Deal BJ, Keane JF, Gillette PC, Garson A. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up. *J Am Coll Cardiol* 1985;**5**:130–5.
3 Friedman WF. The intrinsic physiological properties of the developing heart. *Prog Cardiovasc Dis* 1972;**15**:87–111.
4 Romero TE, Friedman WF. Limited left ventricular response to volume overload in the neonatal period: a comparative study with the adult animal. *Pediatr Res* 1979;**13**: 910–5.
5 Garson A. Medicolegal problems in the management of cardiac arrhythmias in children. *Pediatrics* 1987;**79**:84–8.
6 Gikonyo BM, Dunnigan A, Benson DW. Cardiovascular collapse in infants: association with paroxysmal atrial tachycardia. *Pediatrics* 1985;**76**:922–6.
7 Wolff L, Parkinson J, White PD. Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia. *Am Heart J* 1930;**5**:685–704.
8 Ward DE, Camm AJ. Junctional tachycardias. *Clinical electrophysiology of the heart*. London: Edward Arnold, 1987:173–212.
9 Sperandeo V, Pieri D, Palazzolo P, Donzelli M, Spataro G. Supraventricular tachycardia in infants: use of the diving reflex. *Am J Cardiol* 1983;**51**:286–7.
10 Sreenam N, Wren C. Supraventricular tachycardia in infants: response to initial treatment. *Arch Dis Child* 1990;**65**: 127–9.
11 Garson A, Gillette PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment and long-term follow-up in 217 patients. *J Pediatr* 1981;**98**:875–82.
12 Clarke B, Till JA, Rowland E, Ward DE, Barnes PJ, Shinebourne EA. Rapid and safe termination of supraventricular tachycardia in children by adenosine. *Lancet* 1987;**i**:299–301.
13 Overholt ED, Rheuban KS, Gutgesell HP, Lerman BB, Dimarco JP. Usefulness of adenosine for arrhythmias in infants and children. *Am J Cardiol* 1988;**61**:336–40.
14 Till JA, Shinebourne EA, Rigby ML, Clarke B, Ward DE, Rowland E. Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children. *Br Heart J* 1989;**62**:204–11.
15 Griffith MJ, Linker NJ, Ward DE, Camm AJ. Adenosine in the diagnosis of broad complex tachycardia. *Lancet* 1988;**i**: 672–5.
16 Shahar E, Barzilay Z, Frand M. Verapamil in the treatment of paroxysmal supraventricular tachycardia in infants and children. *J Pediatr* 1981;**98**:323–7.
17 Leitner RP, Hawker RE, Celermajer JM. Intravenous verapamil in the treatment of paroxysmal supraventricular tachycardia in children. *Aust Paediatr J* 1983;**19**:40–4.
18 Soler-Soler J, Sagrista-Sauleda J, Cabrera A, *et al*. Effect of verapamil in infants with paroxysmal supraventricular tachycardia. *Circulation* 1979;**59**:876–9.
19 Radford D. Side effects of verapamil in infants. *Arch Dis Child* 1983;**58**:465–6.
20 Epstein ML, Kiel EA, Victoria BE. Cardiac decompression following verapamil therapy in infants with supraventricular tachycardia. *Pediatrics* 1985;**75**:737–40.
21 Kirk CR, Gibbs JL, Thomas R, Radley-Smith R, Qureshi SA. Cardiovascular collapse after verapamil in supraventricular tachycardia. *Arch Dis Child* 1987;**62**:1265–6.
22 Skovranek J, Ostadal B, Pelonick V, Prochazaka J. Ontogenic differences in cardiac sensitivity to verapamil in rats. *Pediatr Cardiol* 1986;**7**:25–9.
23 Till JA, Rowland E, Shinebourne EA, Ward DE. Treatment of refractory supraventricular arrhythmias with flecainide acetate. *Arch Dis Child* 1987;**62**:247–52.
24 Till JA, Shinebourne EA, Rowland E, *et al*. Paediatric use of flecainide in supraventricular tachycardia: clinical efficacy and pharmacokinetics. *Br Heart J* 1989;**62**:133–9.
25 Janousek J. Diagnostic and therapeutic use of transoesophageal atrial pacing in children. *Int J Cardiol* 1989;**25**:7–14.
26 Sugrue DD, McLaren C, Hammill SC, Gersh BJ, Mair DD, Holmes DR. Refractory supraventricular tachycardia in the neonate: treatment with temporary antitachycardial pacing. *Mayo Clin Proc* 1985;**60**:169–70.
27 Belhassen B, Pauzner D, Blieden L, *et al*. Intrauterine and postnatal atrial fibrillation in the Wolff-Parkinson-White syndrome. *Circulation* 1982;**66**:1124–8.
28 Mehta AV, Pickoff AS, Raptoulis, A, *et al*. Atrial flutter and atrial fibrillation associated with Wolff-Parkinson-White syndrome in childhood. *Pediatr Cardiol* 1980;**1**:197–202.
29 Bolens M, Friedli B, Deom A. Electrophysiologic effects of intravenous verapamil in children after operations for congenital heart disease. *Am J Cardiol* 1987;**60**:692–6.
30 Bink-Boelkens M, Velvis H, Homan van der Heide JJ, Eugelaar A, Hardjowijono RA. Dysrhythmias after atrial surgery in children. *Am Heart J* 1983;**106**:125–30.
31 Krongrad E. Postoperative arrhythmias in patients with congenital heart disease. *Chest* 1984;**85**:107–13.
32 Dunnigan A, Benditt DG, Benson DW. Modes of onset ('initiating events') for paroxysmal atrial tachycardia in infants and children. *Am J Cardiol* 1986;**57**:1280–7.
33 Wolff GS, Han J, Curran J. Wolff-Parkinson-White syndrome in the neonate. *Am J Cardiol* 1978;**41**:559–63.
34 Holmes DR, Danielson GK, Gersh BJ, *et al*. Surgical treatment of accessory atrioventricular pathways and symptomatic tachycardia in children and young adults. *Am J Cardiol* 1985;**55**:1509–12.
35 Crawford FA, Gillette PC, Zeigler V, Case C, Stroud M. Surgical management of Wolff-Parkinson-White syndrome in infants and small children. *J Thorac Cardiovasc Surg* 1990;**99**:234–40.

Archives of Disease in Childhood 1991; **66**: 653–655

CURRENT TOPIC

Persistent infant crying

I St James-Roberts

Thomas Coram Research Unit, University of London Institute of Education, 41 Brunswick Square, London WC1N 1AZ

Correspondence to: Dr St James-Roberts.

Persistent infant crying is a common cause of maternal distress and family disturbance and has been linked with child abuse.[1] In addition, its treatment is expensive of both time and money.[2] Perhaps surprisingly, it is only recently that systematic attempts have been made to quantify and categorise such crying.

Epidemiology of infant crying

Brazelton's original data on 80 American cases in private practice[3] have recently been supplemented by larger scale studies of normal communities in Canada[4 5] and England[6] and by a clinical data set of 68 cases.[6] Important limitations are that all these data stem from maternal diaries and questionnaires combining crying and 'fretting'. There is broad agreement about the following findings:

(1) Crying levels increase from birth to a peak at about 6–8 weeks, following which there is a rapid decline. At two months, average total fuss and crying times of 2–2½ hours/24 hour day have been reported by the three studies. Prolonged crying is common at this early stage, with 29% of Northamptonshire infants crying for three or more hours a day during the first three months, declining to roughly 7–10% thereafter.[6]

(2) Rates of maternal distress and referral parallel these crying figures, so that in the first three postnatal months, 20% of Northamptonshire mothers reported being upset by their baby's crying in the preceding week, and 11% had sought recent clinical referral for such crying. The corresponding prevalences were 7–13% and 3–4%, respectively, during the remainder of the year.[6]

(3) Infant crying is not uniform across the day, but shows a circadian organisation from the first weeks onwards. In the first quarter, crying commonly clusters in the afternoon and evening. Of Northamptonshire infants, 21% were reported to cry for two or more hours between 6 pm and 12 am, declining to 3–5% thereafter.[6]

(4) In the Northamptonshire data, the afternoon and evening clustering of crying declined in the middle of the first year. At the age of 9 months, crying during the night became more common, but was confined to infants who were persistent criers more generally.[6]

(5) Infants referred to health visitors or general practitioners for crying problems cried two to three times longer than the mean community levels.[6] These infants showed the same crying pattern features (such as the afternoon and evening peak) as the community sample, but cried repeatedly throughout the day.

Because maternal observations are central to clinical practice, these figures and the methods used to obtain them seem likely to be useful in primary healthcare.[7] So far as the aim is to draw specific conclusions about infant crying, it is becoming clear that a broader data base, together with clearer distinctions about patterns and types of crying, is needed. Crosscultural data from non-westernised societies are lacking and would help to establish the generality of the crying patterns noted here. To increase precision of measurement 24 hour voice activated tape recordings are useful, both for delineating crying and probing the bases for maternal reports. Although this method has so far been limited to small samples, it has confirmed the validity of two maternal findings: the six week afternoon and evening peak and high crying levels in clinical cases.[6]

Colic

The term 'colic' has three distinct meanings. The first refers simply to the amount and, to a lesser degree, the intensity of infant crying. For instance, the 'rule-of-threes' described by Wessel *et al* defines colic as 'paroxysms of irritability, fussing, or crying lasting for a total of more than three hours a day and occurring on more than three days in any one week'.[8] In this sense the term colic overlaps with the term 'persistent crying' used in the present paper, although no account has been taken so far of the intensity of crying. At present there is no clear reason for the selection of three hours or days of the week for use in definitions and other criteria are also used.

A second use of 'colic' is to designate parental (usually maternal) referral for problem infant crying and associated behaviour.[9] Because the likelihood that mothers will seek referral depends on maternal features and on the accessability of referral services, cases of colic identified in this way will have a different prevalence, and may be of a different type, from those defined by infant behaviour.

The third use, reflecting the implication that colic is a syndrome of gastrointestinal disturbance, infers the existence of pain which is associated with digestion. As Illingworth noted, many reports have been published, which have failed to show intestinal or other abnormalities in infants diagnosed as having colic, so that this approach rests largely on the finding that the anticholinergic drug dicyclomine hydrochloride is an effective treatment in some cases.[10] It is also unclear which aspects of behaviour are indicative of colic pain. For instance, evidence is lacking that colic crying is distinct from more general crying, while symptoms used diagnostically by some clinicians—expelling flatus or drawing up of the knees—are not considered symptomatic by others (H Keller, *et al*. The concept of colic and infant crying in paediatrics. Presented at Third International Workshop on Infant Cry Research, Helsinki, July 1989). Likewise, there are differences of view between nurses and mothers. Mothers link colic more specifically to crying that occurs at a particular time of the day—that is, in the evening (PA Field, D Gojmerac. Mothers' and nurses' idea of colic. Presented at the Third International Child Health Congress, London, March 1990).

Given this lack of consensus about how to define and measure colic, it is not surprising that estimates of its prevalence have ranged from 10 to 40%.[11] Arguably the term's etymological origin (Greek *kolikos*, the adjective of *kolon*) should confine its use to describing digestion related behaviour, in which case effective ways of distinguishing such behaviour are needed. It is unclear why digestion related crying should occur particularly in the evening; there should presumably be a systematic relationship between the periodicities of feeds, of digestive processes, and of related behaviours. One promising line of inquiry stems from the finding that a minority of infants (perhaps 4%) respond to cows' milk whey protein challenges with intense crying. This is consistent with an allergic response, so that if the mechanism can be specified the way is open for the establishment of a specific link between physiological processes and crying, albeit for a small number of infants. In the meantime it is important not to lose sight of a further, psychoprophylactic, use of the term 'colic'. Faced with unsoothable infant crying, many mothers and some professionals use the term to attribute the cause of the crying to short lived disturbances in a normal infant, as opposed to deficiencies of care. In this sense the concept of colic can be useful in alleviating feelings of inadequacy. Where neglect can be ruled out, it may be appropriate to respect this view until a more effective one is available.

Causes of persistent infant crying

PHYSIOLOGICAL DISTURBANCE

Crying is a 'final common pathway' for a variety of illnesses and physiological disturbances, but these are usually detectable by routine clinical practice.[12] Several studies have suggested that crying may be linked with certain suboptimal conditions during pregnancy and birth, but consistent evidence of such a link is lacking.[13] The most promising evidence for an organic reason for infant crying comes from the finding of cows' milk whey intolerance in a minority of cases. Most infants who cry for prolonged periods do not seem to have organic disorders and grow up and develop normally.[11]

TEMPERAMENT

The idea that some infants are constitutionally predisposed to be difficult stems from the New York Longitudinal Study of Temperament.[14] The authors emphasised, however, that difficult temperament is not synonymous with crying, but includes features such as irregularity of biological functions, withdrawal, unadaptability, and intensity of response.[15] Further, crying as an individual characteristic lacks stability, which is generally agreed to be a defining feature of temperament. That is, most studies have found that there is little overlap between the infants who cry a lot during the first quarter and those who cry later in the first year.[16] The stability requirement also means that temperament is unlikely to account for the predominant features of the clinical crying picture, that is, the age related and time of day crying peaks. It is possible that temperament contributes to other aspects of crying, such as crying vigour, or that, for instance, infants who need high levels of stimulation cry if such needs go unmet. Studies on temperament have, however, thrown little light on these issues so far.

MATURATION

Both psychologists and neurologists have proposed that important 'shifts' of neurobehavioural organisation occur at about 3 and 9 months, and it is tempting to link the crying peaks at these ages to such shifts. Central to this approach is the idea that such transitions are a normal part of development, so that the crying is a reflection of the infant's transitional difficulties. In turn, this view highlights the question of what sort of resources, internal and external, the infant needs to complete the transitions effectively.

This conceptual framework is attractive because it deals with the main features of the clinical findings about persistent crying. Two versions have been put forward, with Lester and Boukydis attributing persistent crying to delayed development of the parasympathetic nervous system,[17] and St James-Roberts attributing it to 'jet lag' occasioned by the transition from a four to a 24 hour, diurnally organised, sleep-wake cycle.[18] There is supporting evidence for both theories, but they await a thorough test.

INADEQUACIES OF CARE

Many claims have been made about parental factors that cause infant crying and parents are nowadays faced with an array of often contradictory advice.

An important distinction should be drawn between caretaking variations within and between cultures. Because prolonged crying is a problem in a sizable minority of infants in our society, the question is whether this can be attributed to normal intracultural variabilities in care. There are several arguments against this. Firstly, there is a high degree of stereotyping in how parents respond to infant crying—that is, they generally go through the same sequence of responses (talking, touching, picking up, and so on).[19] Secondly, infants are unstable in their crying patterns, without corresponding variations in parental care.[6] Thirdly, most studies have not found a birth order effect on crying, which suggests that parental inexperience is not a factor.[6] Lastly, in a study of infants referred because of their crying, the parents made more efforts to soothe their infants than other parents. It is notable that parents of control cases did not need to make such efforts: the infants settled themselves.[20]

These findings do not rule out a contribution of methods of caring, and several treatment studies, reviewed below, suggest that care patterns that are relatively uncommon in our culture may limit infant crying. Rather, the findings imply that persistent infant crying can exist in spite of patterns of care that are effective for most infants in our culture.

Prevention and treatment

Dicyclomine hydrochloride was an effective treatment in some cases, but has been withdrawn because of side effects.[10] Double blind control trials have shown that cows' milk whey protein given as formula or breast milk, increases crying in some infants, whereas a diet free of cows' milk reduces crying in such cases.[21] This may be applicable in only about 4% of infants but warrants consideration, particularly if an allergic response is suspected. A hydrolysed casein formula was used and the authors caution against soya based alternatives.

Interventions that focus on mother-infant interaction are also effective. An increased amount of carrying during the first weeks prevents crying, with particularly pronounced effects on the six week afternoon/evening peak.[5] Counselling that focused on responsive, self reliant mothering proved effective as a treatment,[22] and was more effective than a diet that did not contain cows' milk.[23] Carrying and responsive caring have proved equally effective as treatments in other studies.[9]

These studies suggest that both diet and mother-infant interaction are potential areas of treatment. As yet the mechanisms are unclear, so that it is not possible to adopt a treatment selectively. Parent support remains a central goal and the diaries and questionnaires used in recent studies should help parents and professionals to develop a clearer picture of the crying and to identify strategies for coping that meet the family's needs.[4 6]

1 Frodi A. When everything fails: aversive infant crying and child abuse. In: Lester BM, ed. *Infant crying, theoretical and research perspectives*. New York: Plenum Press, 1985: 263–78.
2 Forsyth BW, Leventhal JM, McCarthy PL. Mothers' perceptions of problems of feeding and crying behaviors: a prospective study. *Am J Dis Child* 1985;**139**:269–72.
3 Brazelton TB. Crying in infancy. *Pediatrics* 1962;**29**:579–88.
4 Barr RG, Kramer NS, Boisjoly C, McVey-White L, Pless IB. Parental diary of infant cry and fuss behavior. *Arch Dis Child* 1988;**63**:380–7.
5 Hunziker UA, Barr RG. Increased carrying reduces infant crying: a randomised control trial. *Pediatrics* 1986;**77**: 641–8.
6 St James-Roberts I, Halil T. Infant crying patterns in the first year: normative and clinical findings. *J Child Psychol Psychiatry* (in press).
7 Golton F, St James-Roberts I. Crying rates in infancy: a study in Northamptonshire. *Health Visitor* (in press).
8 Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called 'colic'. *Pediatrics* 1954;**14**:421–35.
9 Barr RG, Hunziker UA, McMullan SJ, *et al*. Carrying as colic 'therapy': a randomised control trial. *Am J Dis Child* 1989;**143**:435.
10 Illingworth RS. Infantile colic revisited. *Arch Dis Child* 1985;**60**:981–5.
11 Lothe L. Studies on infantile colic. Lund: University of Lund, 1989. 128 pp. (Dissertation.)
12 Valman HB. Crying babies. In: Valman HB, ed. *The first year of life*. London: British Medical Association, 1989:76–80.
13 St James-Roberts I, Wolke D. Do obstetric factors affect the mother's perception of her new-born's behaviour? *British Journal of Developmental Psychology* 1989;**7**:141–58.
14 Thomas A, Chess S. *Temperament and development*. New York: Brunner/Mazel, 1977.
15 Thomas A, Chess S, Korn SJ. The reality of difficult temperament. *Merrill Palmer Quarterly* 1982;**28**:1–20.
16 Hubbard FOA, Van Ijzendoorn MH. Maternal unresponsiveness and infant crying: a critical replication of the Bell and Ainsworth study. In: Tavecchio LWC, Van Izendoorn MH, eds. *Attachment in social networks*. Amsterdam: Elsevier, 1987.
17 Lester BM, Boukydis CFZ. No language but a cry. In: Papousek H, ed. *Origin and development of non-verbal and vocal communication*. Cambridge: Cambridge University Press, 1990:2–26.
18 St James-Roberts I. Persistent crying in infancy. *J Child Psychol Psychiatry* 1989;**30**:189–95.
19 Gustafson GE, Harris KL. Women's responses to young infants' cries. *Developmental Psychology* 1990;**26**:144–52.
20 St James-Roberts I. Persistent crying in the first year of life. *British Psychological Society Abstracts* 1989;**1**:39.
21 Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double blind crossover study. *Pediatrics* 1989;**83**:262–6.
22 Taubman B. Clinical trial of the treatment of colic by modification of parent-child interaction. *Pediatrics* 1984;**74**: 998–1003.
23 Taubman B. Parental counselling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomised trial. *Pediatrics* 1988;**81**: 756–61.

PERSONAL VIEW

District handicap teams in England: 1983–8

M C O Bax, Kingsley Whitmore

Community Paediatric Research Unit, Department of Child Health, Westminster Children's Hospital, Vincent Square, London SW1P 2NS
MCO Bax
Kingsley Whitmore

Correspondence to:
Dr Bax.

The need to study a wide range of attributes and functions when assessing a disabled child has long been recognised. The concept of the multidisciplinary investigation of children with behaviour disorders led to the opening of child guidance clinics first in the United States and then in this country in the 1920s. Paediatricians in the 1940s and 1950s were able to pay more attention to the complex chronic disabilities, and special combined clinics were set up. These early ventures led to recommendations about the way such clinics might be run.[1] So in a higgledy piggledy way services for disabled children were beginning, but they were being planned in isolation, and were initially exclusively for children with specific disorders; the notion of a service for all disabled children was embryonic.

The idea of health and education authorities together planning combined facilities for the investigation, treatment, and special education of young, disabled pupils was also new. In the absence of alternative arrangements local education authorities had been opening their own diagnostic and assessment units; these often operated independently of hospital specialist facilities and without appropriate support services.[2 3]

Acting on a recommendation in the Sheldon report on child welfare centres that health authorities should be asked to review their arrangements for the assessment of handicapped children,[4] the then Ministry of Health issued a memorandum containing the advice of 'a small group of experts' on the setting up of comprehensive assessment centres for children with all types of handicap.[5] The ministry set aside special funds to help regional hospital boards finance such centres and by 1973 there were 52 either in existence or being built.

The Court report went further.[6] Concerned at the constant failure of clinics specialising in single disabilities to offer a wide assessment of development and residual functions of referred children, the report recommended that each health district, with the support of local education and social service authorities, should organise formally a multidisciplinary team for all handicapped children as a central feature of its comprehensive services for handicapped children. It was also convinced that these 'district handicap teams' should have integrated facilities for prevention and treatment as well as for assessment, and that they should have an operational role as well as a clinical function. By an operational role the committee meant that the district handicap team should be concerned with other district staff in epidemiological surveys and in the identification of disabled children, and in monitoring its own effectiveness; it should also act as a district resource centre for handicap in childhood.

The committee suggested that the district handicap team should comprise a consultant community paediatrician, a child health visitor for handicapped children, a specialist social worker, a principal psychologist, and a teacher with wide experience of handicapped children of nursery and infant school age. As a secondary (specialist) service the district handicap team would then see the minority of handicapped children who had complex or severe disorders (or both). It would work both within and from a child development centre, which itself would be situated in or near the district's general hospital. It would be in support of similarly integrated primary care services geared to meet the needs of most handicapped children.

The government of the day accepted in principle that 'district handicap teams should provide a framework within which all the needs of the relatively few children with severe handicap, both physical (including sensory) and mental can be met. . .' and it invited health authorities to draw up joint proposals with education and social service authorities for their organisation and operation.[7] As it simultaneously sanctioned the establishment of community teams for mentally handicapped children and adults, however, in practice it clearly had some reservations about relying on district handicap teams to meet all the needs of all severely handicapped children. The recommendation for 'cradle to the grave' community mental handicap teams had been made by the National Development Group (an advisory body set up by the government in 1975 to look at services being offered to mentally handicapped people), which feared that it would be some time before district handicap teams could become operative but community mental handicap teams could be set up at once.

As their report was reprinted in November 1983 we assume it still represents official policy, just as presumably DHSS circular HC(78)5 did, in so far as it has not been officially withdrawn.[8] What influence this departmental ambivalence may have had on the development of district handicap teams (and community mental handicap teams for that matter) must remain a matter for conjecture. We note, however, that in summing up the results of a limited survey of both kinds of team conducted on behalf of the Campaign for Mentally Handicapped People, Plank emphasised the need for district handicap teams to be more clearly based on the Court committee pattern, and for community mental handicap teams to confine their services to adults only.[9]

It was against this background that we had an opportunity to carry out a postal inquiry of every district health authority in England in 1983, supplemented by visits to a few selected districts, to find out how far district handicap teams had been established and how they were working. Of districts contacted, 94% completed a questionnaire. This asked whether the district had a handicap team and also whether it had a children's assessment centre; it went on to ask detailed questions about such units and inquired whether any changes were being planned; it concluded with a request for a brief statement about the overall pattern of services for handicapped children in the district. This first inquiry was sponsored by the DHSS to whom we reported the next year.[10]

In 1988 we again made contact with each health authority (98% replied; two no longer existed after the second reorganisation of the NHS in 1984). They were asked if the changes contemplated for their handicap team or assessment centre had materialised. Districts that had established a district handicap team since 1983 were subsequently asked to complete the original questionnaire that had been issued in 1983. Descriptions of a 'district handicap team' or an 'assessment centre' were checked against those listed in the Social Services Year Book for 1989/90, and discrepancies were investigated by writing to the consultant paediatrician concerned.

It was as a result of these subsequent inquiries that we fully appreciated how much confusion existed as to what is meant by a 'district handicap team'. Looking back this was probably the reason why the questionnaire completed in 1983 gave the impression that there were 119 district handicap teams in England, whereas from information supplied by district medical officers to an initial inquiry we had expected there to be 100 (nine district medical officers did not reply). We had assumed (mistakenly it now seems) that the difference was the result of an administrative rather than a technical error.

In 1988, therefore, we set down the minimum criteria that we felt justified the classification of a unit in 1983 as a Court type district handicap team, and with this in mind we looked again at the questionnaires returned in 1983. The revised results are published here for the first time and differ in important respects from those reported earlier. We also now report on some of the changes that have taken place during the last five years.

Revised analysis of 1983 data

CLASSIFICATION AND DISTRIBUTION OF UNITS

The minimum criteria we adopted for classification of a unit as a district handicap team based on our interpretation of the Court report was: the existence of a multidisciplinary team of practitioners who were personally engaged in the clinical assessment and care of individual handicapped children domiciled within the district, and personally concerned in the team's operational responsibility for providing a regular service. It should also act as a resource centre to other people or institutions caring for such children, and monitor its particular contribution to the district's services for all handicapped children. Applying these criteria in retrospect, only 61 districts (32%) could in our opinion be said to have had a Court type district handicap team in 1983 (table 1).

As a result of this reclassification we encountered two other types of unit calling themselves district handicap teams, neither of which satisfied the above criteria. The first type provided facilities for the clinical assessment (and to some extent care) of handicapped children by a multidisciplinary team of practitioners, but only for those living in the local community; they had not been set up to meet the needs of the district

Table 1 Regional distribution of units (England 1983)

Region	*No of district health authorities*	*No of district health authorities having:*					*No that did not reply*
		District handicap team	*Assessment centre*	*District coordinating group*	*Separate assessment centre and district coordinating group*	*Nil units*	
Northern	16	4	2	4	2	2	2
Yorkshire	17	7	3	0	1	4	2
Trent	12	2	5	1	2	2	0
E Anglia	8	2	1	1	0	4	0
NW Thames	15	4	2	5	1	2	1
NE Thames	16	7	3	2	1	3	0
SE Thames	15	7	3	0	2	3	0
SW Thames	13	3	3	0	5	0	2
Wessex	10	1	3	1	2	3	0
Oxford	8	3	2	0	0	2	1
S Western	11	4	3	2	1	1	0
W Midlands	22	5	11	0	1	4	1
Mersey	10	3	0	4	0	1	2
N Western	19	9	3	1	2	3	1
Total (%)	192	61 (32)	44 (23)	21 (11)	20 (10)	34 (18)	12 (6)
Predominantly rural districts	85	23	19	7	10	20	6
Predominantly urban districts	85	33	21	7	9	5	10

as a whole, nor had they assumed an operational role in respect of handicapped children throughout the district. Forty four districts (23%) had this type of unit; we have classified it as an assessment centre, which is what many of them were actually called (table 1).

The second type consisted of a group of professionals not all of whom were personally concerned in the clinical care of individual children or were even clinical practitioners, but who nevertheless made decisions about the coordinated care or education (or both) of individual handicapped children. Often they would meet and discuss children named on a register, relying on information supplied by other professionals; they may or may not have had an operational role in respect of the district's services for handicapped children. Twenty one districts (11%) had such a group, which we have classified as a district coordinating group in table 1. Twenty districts (10%) had at least one assessment centre as well as a district coordinating group, but the two services did not function together and often there was only one person (usually a doctor) attending both.

A number of districts explained that as they were serving a rural community one central team was seldom appropriate. Quite arbitrarily we picked out 'the predominantly rural' and 'the predominantly urban' districs; by coincidence we found we had selected 85 districts in each group. The distribution of units in these two kinds of district is compared at the foot of table 1. The urban districts were a little more likely to have a district handicap team than the rural districts (39% and 27%, respectively) but the other types of unit were equally common. Rural districts, however, were from two to four times more likely not to have any type of unit at all.

The 1983 questionnaire also asked whether the district had a community mental handicap team; 132 (69%) said they did but of these only 74 (56%) accepted children. Thirty nine of the 192 districts (20%) said they did not have such a team, and 21 did not answer this question.

DISTRICT HANDICAP TEAMS AS OPERATIONAL UNITS

Of the 61 units we reclassified as Court type district handicap teams, 49 (80%) stated who made up their 'core' team. The mean size was seven members (range 3–10); in all, 29 different professions were named and there were 44 different combinations of membership of which only five occurred twice. Certain disciplines predominated (table 2).

We asked if the district handicap team had a 'formal team leader' and 46 (75%) said it did: in 51 (84%) of them a doctor was named, usually a paediatrician rather than a senior clinical medical officer (ratio 2:1). In seven (11%) leadership was shared or rotated among the core members.

We specifically asked about three kinds of operational work. Four out of five district handicap teams met regularly to discuss the way their service was running and plans for the future. Appreciably fewer provided regular services to other people or institutions: 32 (52%) to day nurseries and 10 (16%) to schools. In addition to this team members were quite prepared to see referred children in places other than the child development centre. Thus 44 teams (72%) said they would visit them when necessary at home, 49 (80%) at a day nursery, 42 (69%) at a special school, 38 (62%) at a primary school, and 32 (52%) at a secondary school.

Table 2 Number (%) of district handicap teams (n=61) that mentioned the professionals who were core members

All five disciplines laid down by Court committee	15 (25)
No mention made of:	
Consultant paediatrician	9 (15)
Health visitor	11 (18)
Social worker	17 (28)
Psychologist	19 (31)
Teacher	36 (59)
Others considered core members:	
Physiotherapist	41 (67)
Speech therapist	36 (59)
Senior clinical medical officer	35 (57)
Occupational therapist	29 (48)

The third operational task we asked about was the organisation of seminars and training courses. Forty five district handicap teams did this (74%) though to fulfil our classification of a district handicap team they had to do more than just this; only 24 (39%) undertook all three specific operational tasks.

DISTRICT HANDICAP TEAMS AND ASSESSMENT CENTRES AS CLINICAL UNITS

The clinical functions of a district handicap team are essentially no different from those of an assessment centre. The rest of the information reported here is therefore derived from questionnaires returned to us by the 61 districts we regarded as having district handicap teams and the 64 districts that had assessment centres. We have used the term 'child development centre' to cover all these 125 units that provide a personal clinical service.

Thirty three child development centres (26%) had been functioning for nine years or more (some for as many as 20 years); the same proportion had been open for five to eight years, and the same for one to four years. Eight centres

Table 3 Range and frequency of sessions by professional staff in child development centres

	No (%) of all centres (n=125)	*Average No of sessions (63 centres)*
Seven most commonly named professionals:		
Paediatrician	100 (80)	3·2/week
Senior clinical medical officer	96 (77)	3·2/week
Physiotherapist	101 (81)	6·7/week
Speech therapist	100 (80)	4·7/week
Social worker	85 (68)	4·5/week
Health visitor	84 (67)	2·4/week
Occupational therapist	79 (63)	4·2/week
Four other professionals named by about half the centres:		
Educational psychologist	66 (53)	1·1/week
Clinical psychologist	60 (48)	1·6/week
Teacher	60 (48)	4·4/week
Audiologist	60 (48)	3·0/month
These less often mentioned:		
Nurse	54 (43)	7·6/week
Orthopaedic surgeon	40 (32)	1·3/quarter
Ophthalmologist	28 (22)	1·4/quarter
Mental handicap specialist	25 (20)	1·8/quarter
Child psychiatrist	24 (19)	2·1/month

(6%) had been open for less than one year and the remainder did not say. Eighty (64%) were sited in (or in the grounds of) the district general hospital, and 18 (14%) were in a health service clinic. Fifteen (12%) were separate from both these and 12 (10%) did not say.

Table 3 shows how many centres had regular sessions from certain professionals and (among 63 centres) their average frequency. Ninety three centres (74%) had sessions from both paediatricians and senior clinical medical officers; 38 (30%) from health visitors and nurses; and 36 (29%) from both educational and clinical psychologists. Table 3 also shows the multidisciplinary facilities available at centres, but we wanted to know whether they were used for treatment as well as for assessment. Physiotherapy and speech therapy were carried out in 101 of the centres (81%) and occupational therapy in 94 (75%); day care and remedial teaching was provided in 71 (57%) and 70 (56%), respectively. Table 4 shows the extent to which children received wideranging assessment.

Table 4 Number (%) of child development centres (n=125) offering multidisciplinary assessment to 'most' children

Assessment by:	
Paediatrician	107 (86)
Senior clinical medical officer	90 (72)
Physiotherapist	90 (72)
Speech therapist	90 (72)
Audiologist	81 (65)
Psychologist	79 (63)
Occupational therapist	60 (48)
Teacher	42 (34)

Of the 90 centres at which there were sessions from both a paediatrician and a senior clinical medical officer, in 81 (90%) 'most children' were assessed by both.

Table 5 Problems for which children were referred to 50 child development centres during the previous 12 months

Problem	*No of children*	*% Of total referrals*
Mental handicap (including Down's syndrome, n=344)	1650	25
Learning difficulty	483	7
Developmental delay	391	6
Cerebral palsy	781	12
Spina bifida	278	4
Speech and language	938	14
Vision	313	5
Hearing	270	4
Behaviour	560	9
Epilepsy	417	6
Asthma	236	4
Muscular dystrophy	108	2
Miscellaneous (each less than 100)	161	2
Total	6586	100

Ninety four (75%) of the districts that had a child development centre also had a community mental handicap team, though only 56 (60%) of the latter accepted children. In the 56 districts that had both these facilities, 38 of the child development centres (68%) said that they also saw children who attended the community mental handicap team.

Some centres commented that who the child was assessed by would depend upon the reason for referral. Fifty centres gave information about the number of children with various problems seen during the past year, and the data are summarised in table 5.

Age is an important factor to be borne in mind when looking at the data presented here. We did not feel we could burden the centres by asking the age of each child referred; instead we asked the age range that they accepted. Twenty nine of the 125 centres (23%) would only see children up to the age of 5, 76 (61%) would see any child under school leaving age, and 14 (11%) set various age limits between 5 and 16. Thirty four centres (27%) said they would see young people at least up to the age of 18, and 26 (21%) would see 19–20 year olds if necessary.

The principal sources of referral were paediatric outpatients (n=76, 61%) clinical medical officers (n=59, 47%) and neonatal follow up clinics (n=46, 37%); general practitioners and health visitors were each named by 41 centres (33%). Direct referrals were accepted from health visitors by 47 centres (38%), from social workers by 40 (32%), and from teachers by 31 (25%). Parents had direct access to 36 of the centres (29%); they took part in the running of 21 centres (17%), mainly in organising the toy library.

Table 6 Changes in units and districts between 1983 and 1988

Type of change	*No of units or districts reporting changes and No of changes made*						
	Among 32/61 district handicap teams	*Among 22/44 assessment centres*	*Among 7/21 district coordinating groups*	*Among 11/20 separate assessement centres and district coordinating groups*	*Among 15/34 districts with no facilities initially*	*Among 7/12 districts that did not reply initially*	*Total among 94/192 units or districts*
More sessions from various staff	51	31	4	12	0	0	98
Improvements to accommodation	12	7	0	1	0	0	20
Improvements in facilities	14	5	0	3	0	0	22
Change in classification:							
To a district handicap team	—	0	3	0	—	—	3
To a separate assessment centre and district coordinating group	0	1	0	—	—	—	1
Opened since 1983:							
District handicap team	—	—	—	—	5	2	7
Assessment centre	—	—	—	—	5	4	9
District coordinating group	—	—	—	—	1	0	1
Separate assessment centre and district coordinating group	—	—	—	—	4	1	5
Total No of changes	77	44	7	16	15	7	166

Table 7 Regional distribution of units in England, 1988

	No (%) of district health authorities (n=190)
District handicap team	71 (37)
Assessment centre	54 (28)
District coordinating group	18 (9)
Assessment centre/district coordinating group	25 (13)
Authorities without units	18 (9)
No of authorities that did not reply	4 (2)

CHANGES IN UNITS THAT HAVE TAKEN PLACE SINCE 1983

Among the 146 units identified in 1983 (see table 1) 144 changes had been made by 1988, either in the facilities or in the work done by the unit; these are shown in table 6. This table also shows that by 1988 roughly half the districts that did not have a unit in 1983, and half of those who did not answer our first inquiry, had established a unit of one kind or another; only 24 districts had no such service for their handicapped children.

The changes reported since 1983 were evenly distributed among all types of unit with the exception of district coordinating groups. The most common changes have been an increase in the number of sessions by existing staff, and an increase in the variety of disciplines employed, mainly affecting therapists (60 changes, 42%) and doctors (27 changes, 19%).

Only one third of the units opened during the last five years have been district handicap teams; twice as many have been assesment centres, with or without a district coordinating group. By 1988, therefore, 150 of the 192 district health authorities (78%) had child development centres, of which 71 seemed to be functioning as Court type district handicap teams (table 7).

Discussion

Though it is probably true to say that no two district handicap teams or assessment centres are alike, we believe that the data presented here give a reasonably accurate picture of current national trends. They raise some important questions, and we hope our answers will provoke discussion on the future pattern of centres locally.

In this discussion—as in the introduction—there may seem to be some inconsistency in our use of the terms 'disabled' and 'handicapped'. The World Health Organisation[11] has emphasised the distinction between them (with which we agree) but this was made after the publication of the Court report. We have retained the description 'handicapped children' when this has been correct in the historical context though 'disabled children' would be a more exact description using current, accepted terminology.

QUESTIONS ARISING FROM THE INQUIRY

De we need Court type district handicap teams?

In the 10 years between 1973 and 1983 the number of health authorities with special centres for handicapped children had more than doubled, but barely half of them seemed to be functioning as full district handicap teams. Of the 22 centres established during the last five years of which we have information, only seven can in our opinion be regarded as district handicap teams. Why is this so?

We know that not all doctors like the idea of working in a formally designated multidisciplinary team. Some think it constricting and time consuming; they prefer the traditional pattern of being free to work as independent practitioners making referrals when necessary to specialists in other disciplines with whom they have built up liaisons. Others who are not averse to the multidisciplinary approach maintain that when this becomes formalised into the establishment of recognised teams (as in district handicap teams and child guidance (psychiatric) clinics) there is an unacceptable risk of the ultimate clinical authority and responsibility for the patient's care passing out of the hands of the doctor, with whom (they argue) it should always reside as the most highly trained member of such teams.[12] We are not impressed by either of these objections.

District handicap teams owe their origin to the need for routine multidisciplinary investigation of seriously handicapped children. Responsibility for the whole child, therefore, has to be shared between the professionals assessing the various aspects of the case. Doctors particularly may find this difficult because their training does little to prepare them for the problems that commonly arise in establishing effective interdisciplinary collaboration and decision making.[13] These problems are seldom insurmountable, and both district handicap teams and child guidance clinics have surely stood the test of time as multidisciplinary units.

We suspect, however, that one of the main reasons why there are not more district handicap teams is because there is a misunderstanding about what they are supposed to do. A number of districts thought that such teams should not have such wide ranging responsibility because (as one doctor put it) 'it needs front line people having the ear of managers' for it to be carried out successfully. Others saw a danger that the district handicap team would be regarded as responsible for the coordination and planning of services for handicapped children, whereas this was the function of a child health care planning team. Some districts said they did not have a district handicap team because they had a team for planning of services for handicapped children, while others admitted that their so called 'district handicap team' had only an administrative function.

This confusion is surprising, as the Court committee quite clearly stated that it deliberately described the second function that it had in mind for the team as operational and not administrative so that it should not be thought that it was implying that a district handicap team should usurp the roles of senior doctors and nurses whose job it was to manage services.

We think that the Court committee's concept of a district handicap team was sound, but as the term itself has clearly proved to be open to abuse and is therefore redundant we suggest it should be shelved. What alternatives are there? For a number of reasons some units are called assessment centres, but the notion of specialist centres concentrating on assessment was already obsolete in 1974. We can well understand why the Court committee preferred the name 'child development centre' as the base for their district handicap team. Purists might argue that even this is a misnomer because it specialises in disability rather than in development, and disability is not a term that should cause offence as handicap sometimes does.[14] This description is now widely used, however, and it seems sensible for district handicap teams to be referred to in future as child development centres, though such centres must assume both a clinical and operational role.

Where should child development centres be based?

It is logical that the first step in the investigation of a disability in a young child should be a medical diagnosis; it is therefore understandable why in the past health authorities should have taken the initiative in setting up district handicap teams. It is equally sensible for them to be situated in, or within the environs of, the district general hospital where all the necessary specialist medical expertise and facilities are to be found. There are, however, other considerations. The extent to which treatment can be provided depends not only on cooperation among the relevant disciplines but also on having accommodation for them to work in. The inconvenience and often difficulty that parents and children have travelling from a distance may be acceptable for one or two visits for diagnosis and assessment, but would be intolerable for repeated visits for treatment. In addition, facilities that may be appropriate for young children may not be so for older ones. Arrangements for seeing children obviously need to be as flexible as possible, but even flexible services need a base. We think there really is no better base for a child development centre than in the premises of—or adjacent to—the district general hospital.

A separate purpose built centre is the ideal; for most districts this is out of the question but satisfactory accommodation for nursery education and treatment have to be among the priorities. There are four principal ways of making arrangements more flexible, especially for centres that serve more rural populations. Professional staff may examine a child on their own and make their own initial assessment at any place that is convenient for both parties (which might be at home, in a health service clinic, or in hospital); they then meet to discuss their findings and agree on a course of action. Key disciplines may even be able to operate regularly in satellite centres—for example, in clinics or a subsidiary hospital—in which there is sometimes room for a nursery group. In some districts local education authorities provide accommodation for nursery children or even slightly older ones—for example, in an educational psychology unit with a day teaching unit attached and somewhere for the teacher and visiting staff to confer. Finally, joint examination and assessment (particularly by occupational, speech, and physiotherapists) is gaining clinical favour and obviously has advantages regarding accommodation and staff time.

Some child development centres have special rooms for physiotherapy, others do not, but on our visits we often saw the physiotherapist in the classroom helping the teacher and care staff with the management of children with physical disabilities. Many of them too accepted the need to work mainly through the parents and therefore paid visits to the children's homes. We gained the impression that speech therapists were less inclined to be closetted in the old fashioned speech therapy room that was a feature of the early assessment centres and were more often working in groups or seeing a child and parent or teacher together and discussing ways in which they could all stimulate communication. Unfortunately we asked no questions about Portage schemes but we became aware that many centres were running Portage systems with the mentally handicapped children, and they were doing this in various ways. A Portage system is, of course, carried out in the young child's home; in some centres the psychologist supervised the training of parents and others caring for the child, while in others a health visitor specialising in handicap paid weekly visits to the home.

What age range should child development centres cater for?

In almost a quarter of the districts referral to the child development centres was restricted to preschool children. As the presence of severe disability is usually recognised during the first few years of childhood child development centres understandably have a heavy load of preschool children, but there are still some children in whom serious disability is not diagnosed until after the age of 5. The full investigation of such children, whether they be in ordinary or special schools, should be done by staff at the child development centre, both in the centre and on visits to schools. Such visits are also important in maintaining continuity in the care of children who first attended the centre before they started school; we expect severely disabled children to remain on the centre's register throughout their school years.

The fact that one in four child development centres are open to adolescents is a measure of the long term interest and commitment of paediatricians for handicapped children whom they have known for many years, but it is also a sad commentary on the state of suitable services for this age group. Those who are mentally handicapped can transfer to community mental handicap teams, but child development centres become increasingly inappropriate as a source of health care for physically handicapped teenagers and after leaving school there may be no facilities at all for them.[15] While this situation continues it would be wrong for us to suggest there should be any arbitrary age limit, even of 16, for attendance at a child development centre.

Should child development centres be able to deal with all kinds of disability?

Because of the importance of a multidisciplinary assessment of children who seem to have only one serious or complex (or both) disability, we believe that initial referral to a child development centre is the preferable route to diagnosis and treatment of all disabled children. There are certainly rare disorders for which onward referral to a specialised or regional clinic might be necessary. Most of the less rare but serious disorders, however—even those affecting vision and hearing—can usually be dealt with effectively within a child development centre provided that there is accommodation for, and sessions from, the appropriate specialists. Child development centres can only deal with the 2% or so of children with disorders that give rise to chronic disability—that is, an actual or potential handicap to the child. The children with epilepsy and asthma (amounting to almost 10% of referrals, table 5) may have had extenuating circumstances that required the expertise of the child development centre, but many of them may have been inappropriately referred.

Many of the children attending child development centres in 1983 also had behaviour problems, and helping with difficult behaviour is a major part of a child development centre's work. From our visits we discovered that some children had undoubtedly been referred to child development centres as more likely sources of help in dealing with difficult behaviour than that obtained in a family therapy or an analytically oriented child psychiatric clinic. In other cases the referring doctor had thought that the child development centre was initially the appropriate place because of a strong possibility of organic disease being the cause of the behaviour problem.

Two fifths of children referred to child development centres had learning problems. Does the nature of this disability warrant duplicating or even overlapping facilities between child development centres and community mental handicap teams? We think not. Not all children with learning difficulties are mentally handicapped and referral to a community mental handicap team would not normally be an appropriate way of investigating developmental delay and excluding intellectual retardation; child development centres are well equipped to do this. Furthermore, many of the severely handicapped retarded children have physical or sensory disorders (or both) and need the facilities for diagnosis and treatment that are in or adjacent to most child development centres. We think it is wrong to segregate the investigation and assessment of children likely to be intellectually retarded, or even certain to be (as in Down's syndrome) from those who probably are not; they need paediatric services because of their age rather than mental handicap services because of their disability.

We therefore join Plank in endorsing the Court committee's recommendation that all mentally handicapped children be catered for in the first instance in child development centres.[9] Only exceptionally should it be necessary for the most severely disabled children to attend a community mental handicap team, and then mainly for health care. These teams should concentrate on services for adolescents and adults.

We anticipate that 1 to 2% of the children referred become regular clients of a child development centre. There is a further, perhaps similar, proportion of children referred for diagnostic advice and assessment whose disabilities do not prove to be severe enough to warrant regular attendance at the child development centre.

What professional staff does a child development centre need?

If a child development centre is to be able to investigate any kind of severe or complex disability, who are the professionals who need to have regular weekly sessions, and who should visit less often?

There can be no argument about the need for weekly sessions for a social worker and teacher, and we think the need for the teacher has to be emphasised. But what about the therapists? As the Court committee were so convinced of the need to provide and coordinate treatment as well as assessment (and rightly so) it is surprising that it did not name any therapists as core members of the district handicap team. Our data show that in practice about 60% of child development centres regard physiotherapists and speech therapists as core members, and we feel sure that all child development centres should have weekly sessions from them as well as from an occupational therapist.

Doctor, nurse, and psychologist commonly have dual representation in child development centres. Often both the paediatrician and the senior clinical medical officer examine a child; several reasons are given for this (including the fact that the senior clinical medical officer is usually able to do Griffiths's tests), but is it really necessary? We think not. It may of course be a transitional anomaly now that the Court committee's recommendation for the appointment of consultant community paediatricians is slowly being implemented. Having only one key doctor will not, of course, reduce the total number of medical sessions required by a child development centre.

The Court committee also recommended there should be only one kind of clinical community nurse in the child health services with responsibility for both preventive and curative care—a child health visitor; as additional training in the care of handicapped children would be a requirement, some of the them would have already worked in district handicap teams. This recommendation for child health visitors was never accepted by the nursing profession and the choice of nurse for child development centres has been between a nurse and a health visitor, with sometimes both being available. Only two out of five centres have been employing nurses, but in those that did they seem to be indispensable, with more sessions each week than any other discipline. Furthermore, most of the centres that had nurses also had liaison health visitors. It is difficult to imagine how one person could effectively carry out the duties of both attendant nurse and liaison health visitor, and how some centres managed without either.

It was the hope of the Court committee that the principal psychologist in the core team of five would be a child psychologist with the combined expertise of an educational and clinical psychologist experienced in working with children. Unfortunately this has not happened. We recognise the official role of the educational psychologist in preparing statements for the children needing special education, but the diminishing importance attached to the end point of intelligence testing—especially in children of nursery school age—and the need for more specialist expertise in the management of children with emotional and behavioural difficulties, make the need for weekly sessions from a clinical psychologist the priority if there has to be a choice.

Of the visiting specialists we think there can be no doubt of the need for a limited number of sessions from children's audiologists, ophthalmologists, and orthopaedic surgeons. In 1983 half the child development centres had audiological support (on average three sessions/month) but two thirds had no orthopaedic sessions, and 80% had no help from an ophthalmologist.

The number of child psychiatric sessions was even more unsatisfactory, yet the prevalence of behaviour problems among disabled children certainly justifies frequent visits from a psychiatrist. Only 19% of child development centres had such sessions in 1983 and then on average only two/month.

The current vogue for family therapy does not seem to us to be particularly effective in helping parents to deal with behaviour problems associated with other disabilities; perhaps this is the reason for what one paediatrician described as 'the boomerang syndrome': send such children to the child psychiatrist and they bounce right back. Behavioural approaches seem to have more to offer and in practice we found many of the children being helped by the centre's psychologist. Unfortunately half the child development centres had no sessions from any kind of psychologist and those that did averaged only 1·5 sessions/week.. Given the range of tasks they have to undertake this is too few for them to become personally concerned in the treatment of many children. There is clearly a need for child development centres to have more sessions from psychologists and child psychiatrists with special interests in the difficulties of the disabled children present.

Who should refer children to child development centres?

The Court committee appreciated early on that there was a need for parents to be recognised as partners in the process of assessment and decision making, and as front line therapists, in the care of their handicapped children; they therefore stated that parents should have the right of direct access to district handicap teams. This view is not shared by most child development centres today, which (like most specialist services) accept referrals only from doctors.

This is of course a customary privilege that has its roots in medical etiquette, but it is frequently proclaimed as being 'in the patients' best interests' while conveniently husbanding secondary care resources. We do, however, question both the need for and the ethics of imposing restrictions on parents' access to child development centres, especially as not all the specialist expertise that they dispense is medical. The bogey is often paraded of 'creating a precedent by allowing parents direct access and thus opening the floodgates', but in practice this does not happen and it is unlikely that one in three child development centres would still pursue a policy that led to serious overloading of the service. Most parents do not seem to object to referral only by doctors, and there is much to be said for an initial paediatric opinion being sought about any disability before referral to a child development centre; it does guard against the unnecessary and uneconomical use of scarce resources. Nevertheless, for parents who cannot for one reason or another accept this formality, denial of direct access looks like denial of patients' rights and may put the child at risk.

We believe it is as unwise as it is unnecessary for a child development centre to refuse the occasional direct referral of a child by the parents or by any professional concerned in the care of that child. The ethical, administrative, and practical difficulties it presents can almost invariably be overcome by sympathetic, diplomatic, and sensible handling by centre staff.

Who should fund child development centres?

The government has accepted that district handicap teams should be a multiprofessional service jointly organised and operated by health, education, and social service authorities. Though we know of at least two child development centres that are jointly funded our questionnaire did not ask about funding, only about staffing. One cannot assume that because a child development centre does have sessions from professionals employed by local education and social service authorities they are funded by those authorities, but one can be sure that if it does not the centre is unlikely to be jointly funded. It seems, therefore, that social service authorities are not contributing to the service provided by one third of all child development centres and (more seriously, we think) local education authorities are not contributing to half of them.

The crucial role of health authorities in the early identification and diagnosis of disability is reason enough for health authorities to have taken the initiative in setting up child development centres. On the other hand, local education authorities have had a long standing legal responsibility (strengthened by the Education Act 1981) for ascertaining and meeting the special educational needs of handicapped children from the age of 2. This makes it imperative for professionals in health and education services who see such children to work closely together. It seems to us that local education authorities are under a strong obligation to share in funding the staff and facilities required for the proper assessment and treatment of young handicapped children.

When a disabled child reaches the age of 5 the focal point of service has to shift to the school. From this age at least, health and social services must reciprocate by funding adequately their professionals' sessions in the school. It was disappointing to find that in 1983 only half the districts did this in respect of children who first attended their child development centres in their preschool years; only one in 12 seem to be doing so regularly for other disabled children.

Recommendations

By 1988, only 37% of health districts had what we regard as a district handicap team as described by the Court committee. We think that its concept of such a team was sound, but in future it should be exclusively referred to as a child development centre. Every district should have a child development centre and we highlight its essential features by updating some of the Committee's original recommendations as follows:

(1) The child development centre should be closely associated with the district general hospital but equally committed to providing a peripatetic service in satellite premises (especially in rural areas and in selected schools).

(2) Given this assurance, local education and social service authorities should be prepared to enter into joint arrangements for funding and staffing the child development centre.

(3) The child development centre should initially be able to cater for the needs of all children under 10, and for older children in the absence of adequate, similar facilities for disabled adolescents.

(4) The child development centre should be able to provide initial assessment and treatment for children with any kind of disorder, leaving community mental handicap teams to concentrate on the continuing special needs of mentally handicapped adolescents and adults.

(5) To meet this demand, the child development centre should have regular weekly sessions from a consultant community paediatrician, a liaison health visitor, another nurse, a social worker familiar with the needs of disabled children, a psychologist with expertise in the cognitive assessment of disabled children and the management of emotional and behavioural difficulties, a teacher, a physiotherapist, speech therapist, and an occupational therapist, all of whom should be experienced in working with such children.

(6) The child development centre should also have at least one session a week from a child psychiatrist and regular (though not necessarily weekly) sessions from children's orthopaedic, ophthalmic, and audiology specialists.

(7) The referral of children to a child development centre should normally be initiated by a general practitioner, a paediatrician, or another medical specialist, but the centre should also adopt the policy of open referral from parents and any professional attending the child.

(8) As well as providing a clinical service, a child development centre should be prepared and equipped to act as a district resource and information centre for disabled children, and to contribute to the inservice training of all professionals in the district who may play a part in the care of disabled children.

(9) The child development centre should take part in the district's epidemiological studies relating to disabled children and help to monitor the service it provides.

The initial study was undertaken when MCOB was supported by the DHSS, whose help we acknowledge. The views expressed are those of the authors and not of the DHSS. We thank Joy Allsop not only for typing the manuscript but for helping us with the analysis.

1 National Spastics Society. *Organisation of diagnostic and treatment clinics for cerebral palsied children.* Cerebral Palsy Bulletin, Supplement No 4. London: National Spastics Society, 1961.

2 Whitmore K. An assessment service for handicapped children. *Medical Officer* 1969; No 3199, Vol CXXII, No 20: 263–7.

3 Department of Education and Science. *Diagnostic and assessment units.* Education Survey 9. London: HMSO, 1970.

4 Ministry of Health. *Child welfare centres. Report of the subcommittee.* London: HMSO, 1967. (Sheldon report.)

5 Ministry of Health. Momorandum on comprehensive assessment centres for handicapped children. London: Ministry of Health, 1968.

6 Report of the Committee on Child Health Services. *Fit for the future.* Vol 1. London: HMSO, 1976. (Cmnd 6684).

7 Department of Health and Social Security. *Health services development: Court report on child health services.* (HC (78) 5/LAC (78) 2.) London: DHSS, 1978.

8 National Development Group. *Mentally handicapped children: a plan for action.* National Development Group, Pamphlet No 2. London: DHSS, 1977.

9 Plank M. *Child development centres—teams for mentally handicapped people.* London: Campaign for Mentally Handicapped People, 1982.

10 Bax M. *District handicap teams: structure, function and relationships.* London: DHSS, 1985.

11 World Health Organisation. *International classification of impairments, disabilities and handicaps.* Geneva: WHO, 1980.

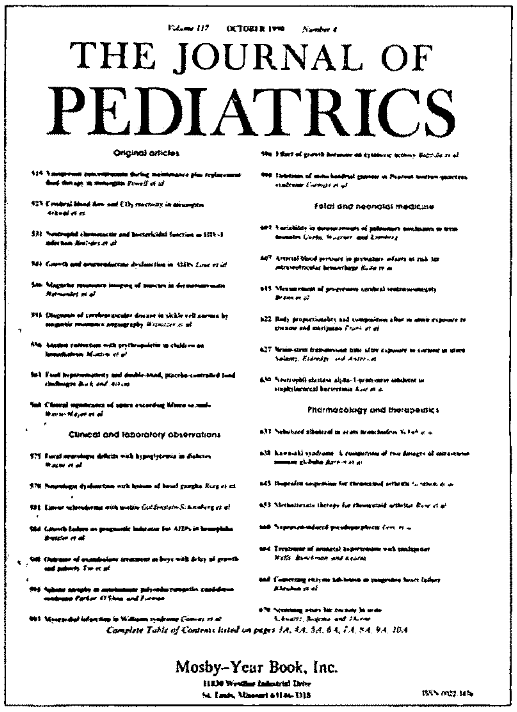
12 Appleyard J, Maden JG. Multidisciplinary teams. *BMJ* 1979; ii:1305–7.

13 Pearson PH. The interdisciplinary team process. *Dev Med Child Neurol* 1983;25:390–5.

14 Committee of Enquiry into the Education of Handicapped Children and Young People. *Special educational needs.* London: HMSO, 1978. (Cmnd 7212.) (Warnock report).

15 Hirst M. *Transfer to adult services: some preliminary findings.* University of York Social Policy Research Unit. (172, 11/83 MH.) London: DHSS, 1983.

SISTER JOURNALS—UNITED STATES



Volume 117 OCTOBER 1990 *Number 4*

THE JOURNAL OF
PEDIATRICS

Original articles

Clinical and laboratory observations

Fetal and neonatal medicine

Pharmacology and therapeutics

Complete Table of Contents listed on pages 1A, 4A, 5A, 6A, 7A, 8A, 9A, 10A

Mosby–Year Book, Inc.

Journal of Pediatrics

As an immediately postwar child, I recall nostalgically the arrival at my home of food parcels from relatives in the United States. No doubt the food itself was welcome but what is impressed upon my mind were the extravagantly glossy and brightly coloured advertisements in the magazines used as wrapping.

I am reminded of these promises of a more glamorous life when obtaining my monthly fix of the *Journal of Pediatrics*—an addiction now well into its second decade. The September 1990 issue is no exception with two aggressive 'puffs' for commercial preparations of surfactant, the second consuming six pages. The United States equivalent of the data sheet for Exosurf, printed in its entirety, albeit almost invisibly for the evolving hypermetrope, is in itself an education both in neonatal physiology and ethical advertising.

The *Journal of Pediatrics* can be relied upon to provide details of meticulously prepared research studies. I forgive it repeatedly that a sledgehammer may be used to crack a nut and that, if pagination is any guide, it often takes at least double the number of blows that the more economical *Archives of Disease in Childhood* might have used.

September's issue is a serendipitous choice in that the first paper is by our own Roy Meadow. (By 'our' I don't mean Leeds where he is professor but Banbury where he was once a general practitioner.) His paper is on suffocation, recurrent apnoea, and sudden infant death; does this mean he will now encounter vituperative press coverage Stateside to add to that provoked in the UK by those who point out that not all parents are squeaky clean? Incidentally, those who believe the major fault of American journals is their insularity should note that of the 32 papers in the September issue, eight are from Europe, two from Africa, and two from the Americas outside the United States.

As a generalist without registrars to keep me up to date but with an army of managers who leave me little enough time to practise medicine let alone read about it, I have to be carefully selective. Of the 32 papers I rated six worth keeping complete and six worth keeping for their summary—including the one I kept simply because it quoted me in its references, a rare citation for a largely commercial scribbler; this is a hit rate of 40% which must be hard to beat.

About the only groups who will find little for them here are the community paediatricians and child psychiatrists, although both might be bemused by the paper entitled 'Dermatoglyphics in children with abdominal pain and constipation'.

The *Journal of Pediatrics* takes itself pretty seriously: there are none of the jokey one liners of its sister transatlantic specialist journal or the historical delvings of the *Archives*. It's surprisingly cheap at about £3·50 an issue including air mail postage so all those advertisements must be worthwhile; especially one seeking a paediatrician in Phoenix, Arizona offering 'excellent fringe benefits including paid malpractice'.

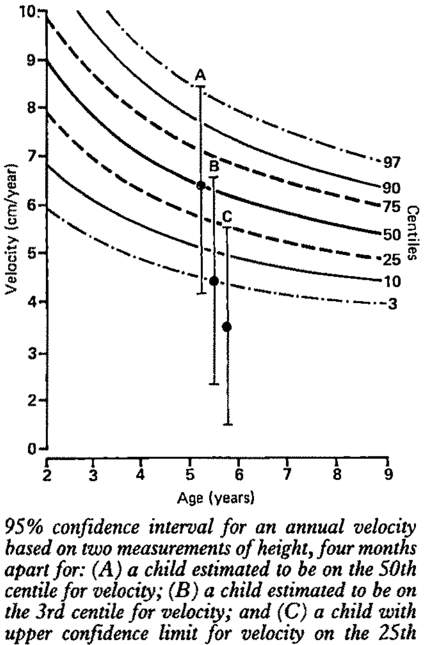
HARVEY MARCOVITCH

LETTERS TO THE EDITOR

Tests for growth hormone secretion

SIR,—The reproducibility of pharmacological and physiological tests for growth hormone deficiency is rightly questioned in the annotation by Brook and Hindmarsh.[1] The authors, however, do not consider the reproducibility of the measurement of height. We recently demonstrated the unavoidable imprecision of height measurement,[2] and emphasise here its serious implications for the interpretation of short term growth data. We are particularly concerned about the estimation of velocity, where the errors from two height measurements rather than one are involved.

In their 'plan for action', Brook and Hindmarsh advise: 'Measure the child and . . . measure the child again after four months and calculate the annual velocity'. To base a velocity on measurements four months apart greatly increases the error of measurement already associated with the estimation of velocity over 12 months. It has been shown that the SD for a single height measurement made by experienced observers lies in the region of 0·25 cm.[2-5] (Any claim of a lower SD may well imply correlated measurement errors, as will happen, for example, if the calibration trials are not blind.) Given a typical SD of 0·25 cm, the 95% confidence interval for an annual velocity, calculated from the formula $2\ (SD)\sqrt{2}$, is the observed increment ±0·71 cm/year. Where the measurements are only four months apart, instead of the standard 12, the confidence interval for an annual velocity triples in length. On this basis, the 95% confidence interval for a child between the ages of 5 and 6 years, estimated to be growing, for example, at the 50th centile for velocity, would lie between 4·2 and 8·4 cm/year, and more than span the whole centile range on the chart (A on the figure). A four month velocity cannot give any indication of current growth.



95% confidence interval for an annual velocity based on two measurements of height, four months apart for: (A) a child estimated to be on the 50th centile for velocity; (B) a child estimated to be on the 3rd centile for velocity; and (C) a child with upper confidence limit for velocity on the 25th centile. The observed velocity lies below the first centile.

Furthermore, we have shown,[6] and the authors have previously stated,[7] that there is little correlation between successive height velocities. Velocity cannot therefore in practice be used to predict future growth.

The appeal of velocity lies in the label it provides. The label 'slow grower' tends to generate action, which is often expected of the clinician, but whether the label is appropriately applied is seldom questioned. The Middlesex height velocity assessment chart—indeed any velocity chart—while attractive conceptually, may be deceptive clinically. We are sure that the authors, in their advice as to when to take 'immediate action', did not mean to imply that where a single four month velocity lies below the third centile, the paediatrician should seriously consider the 'option of . . . giving the child growth hormone'. A velocity, estimated to be on the third centile, could in reality be as high as the 60th (B on figure). To be 95% confident, after only four months, that a 5 year old was growing slowly—that is, at a rate below the 25th centile for velocity, the annual velocity would have to be less than 3·5 cm/year (C on figure). This cut off point lies well below the first centile, and not the 20th as illustrated on the Middlesex chart.

We would again recommend that those involved in the measurement of children establish their own error, in the way we have suggested, and verify for themselves the serious limitations of short term velocity in the assessment of growth.[2] There are no short cuts to replace the need for long term monitoring.

L D VOSS
B J R BAILEY
P R BETTS
The Wessex Growth Study
Room CD53,
Southampton General Hospital,
Southampton SO9 4XY

LDV is supported by Kabi Pharmacia UK Ltd, Sweden AB.

1 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;**66**: 85–7.
2 Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement. *Arch Dis Child* 1990;**65**:1340–44.
3 Tanner JM. Physical development. *Br Med Bull* 1986;**42**:131–8.
4 Preece MA. The anthropometric considerations in the evaluation of growth-prompting treatments. In: Ranke MB, Bierich JR, eds. *Paediatric endocrinology—past and future.* Munich: MD-Verlag, 1986.
5 Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age. *Helv Paediatr Acta* 1988;Suppl 52:3–33.
6 Voss LD, Walker J, Lunt H, Wilkin TJ, Betts PR. The Wessex Growth Study: first Report. *Acta Paediatr Scand (Suppl)* 1989;**349**: 65–72.
7 Brook CDG, Hindmarsh PG, Healy MJR. A better way to detect growth failure. *BMJ* 1986; **293**:1186.

Professor Brook and Dr Hindmarsh comment:
The comments from the Southampton group are noted. As the article was directed at tests of growth hormone secretion our interests lay in the brief given rather than a discussion of errors of height measurement, which, as the authors point out, have been documented by groups in Switzerland and the United Kingdom. As they show, short term measures require different charts for decision making. In practice, however, growth rates less than the third centile nearly always indicate a clinical problem so we stand by our plan.

It should be pointed out that growth velocity is better estimated by linear regression of all measurements obtained over a 12 month period and not based on the extremes of the measurement period which will lead to the sort of errors discussed. The advantage is that all data points are used, including multiple measures on the same day. Growth velocity can then be calculated with an estimate of error.

A disproportionate emphasis is still placed on endocrine tests in establishing the need for growth hormone treatment. Our annotation sought to put this in perspective. As the Southampton group have demonstrated, growth measures are a lot more reliable than any of the current tests available for estimating growth hormone secretory status, placing auxology foremost in the assessment of growth and its disorders in children, even with the inaccuracies to which they have rightly drawn attention.

Gut blood flow velocities in the newborn

SIR,—We read with interest the study by Coombs *et al* of the effects of parenteral indomethacin on splanchnic blood flow.[1] However we were surprised that no mention was made as to how the patency of the ductus arteriosus was established. In describing both the study and control groups the terms 'symptomatic' and 'clinical' lead to the assumption that echo Doppler cardiography was not performed. Surely in order to determine accurately the effect of a patent ductus arteriosus on splanchnic blood flow, with or without parenteral indomethacin, it is essential to assess accurately the direction of flow and the pressure gradient across the ductus for both systole and diastole. The statements that: (1) indomethacin has effects on splanchnic flow independent of its actions on the ductus and (2) the slow administration of parenteral indomethacin shows no apparent loss of efficacy on ductal closure, cannot be concluded from this study and are potentially misleading due to the lack of accurate haemodynamic documentation.

E BRUCKHEIMER
J GLASER
Department of Pediatric Cardiology,
The Shaare Zedek Medical Center,
Jerusalem 91031,
Israel

1 Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: Effects of patent ductus arteriosus and parenteral indomethacin. *Arch Dis Child* 1990;**65**:1067–71.

Dr Coombs comments:
While echo Doppler cardiography may be the gold standard for diagnosing a patent ductus arteriosus, most UK neonatologists when deciding on the need for treatment rely, as we did, on the clinical findings of a characteristic murmur, bouncy pulses, a wide pulse pressure, an increase in oxygen requirements, and evidence of heart failure. These clinical findings were present in all the babies comprising the study group and were not seen in the control group. Supporting, but not influencing, the clinician's decision to treat was the finding in the babies studied of the absence of retrograde diastolic flow in the superior mesenteric artery, an indication of left to right shunt.

The same criteria for ductal closure—disappearance of murmur, return of pulses to normal, and resolution of heart failure—were used in both studies and correlated with the return of diastolic flow. Although the numbers are small, there was no apparent difference in the efficacy between bolus and slowly infused indomethacin.

Our findings are that bolus indomethacin resulted in a pronounced fall in blood flow velocity in the superior mesenteric artery. We believe this fall in velocity represents a local vasoconstriction. This view is supported by animal and human data[1–3] and the observation that the magnitude of fall in velocity was different in the two vessels studied.

The important messages, however, are that with a patent ductus arteriosus the splanchnic blood flow is compromised, and that slowly infused indomethacin avoids the profound fall in gut blood flow velocity that is seen with the first bolus dose of indomethacin.

1 Lippton HL, Armstead WM, Hyman AL, Kadowitz PJ. Characterization of the vasoconstrictor activity of indomethacin in the mesenteric vascular bed of the cat. *Prostaglandins Leukotrienes Med* 1987;**27**:81–91.

2 Feigen LP, King LW, Ray K, Beckett W, Kadowitz PJ. Differential effects of ibuprofen and indomethacin in the regional circulation of the dog. *J Pharmacol Exp Ther* 1981;**219**:679–84.

3 Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol Scand* 1983;**117**:203–11.

Modern management of pyloric stenosis—must it always be surgical?

Sir,—The paper by Eriksen and Anders[1] and the commentary[2] interested us because the management of pyloric stenosis has often provoked controversy. In 1986 we also audited 62 cases presenting between 1979–85 to a mixed paediatric medical and surgical ward outwith the specialist paediatric surgical unit. Preoperative fluid and electrolyte replacement was managed by paediatricians and operations were performed by general surgeons. Prophylactic antibiotics were not given routinely.

Complications in our infants compare favourably with those of the two other recent series (see table).[1 3]

Our audit emphasised the point made by all three contributors,[1–3] that the diagnosis of pyloric stenosis is not always straightforward. It also varies considerably in severity and so it was gratifying that Dr Jacoby's work[4] was quoted by Mr Kiely.[2] Although Jacoby operated on 104 babies with minimal morbidity and mortality there were a further 101 who tended to present later, have less severe vomiting, showed less weight loss and dehydration, and who responded rapidly and successfully to atropine methonitrate (Eumydrin).

In our series of 62 babies, seven were treated successfully with Eumydrin, had a very short hospital stay, and were treated predominantly as outpatients for a mean of seven weeks (range 2–16). In 1987 Eumydrin was taken off the market, having been in use for 60 years. Paediatricians were thus denied the opportunity of avoiding surgery with its 24–50% complication rate. We would like to report that the product Piptalin (Boehringer Mannheim), which contains the antispasmodic pipenzolate bromide, has been used successfully in three babies with pyloric stenosis in the past 12 months. Nowadays few junior staff have any experience of judicious medical treatment for pyloric stenosis. Babies are, therefore, referred without a second thought for surgery, which fortunately carries a negligible mortality, although the complications described above should not be ignored.

Should medical treatment for pyloric stenosis be totally abandoned?

Complications of pyloric stenosis

	Zeidan et al[3] *(1980–5, n=106)*	*Eriksen and Anders (1984–9, n=46)*	*Present series (1979–85, n=55)*
Perforated duodenal mucosa	9	11	6
Wound infection or abscess	6	7	7
Persistent vomiting	9	2	3
Wound dehiscence	0	2	0
Incisional hernia	0	1	1
Haemorrhage	1	0	0
Need for second pyloromyotomy	0	0	1
Total No (%) complications	25 (24)	23 (50)	18 (33)

P G F SWIFT
J E PROSSOR
Department of Paediatrics,
Leicester General Hospital,
Gwendolen Road,
Leicester LE5 4PW

1 Eriksen CA, Anders CJ. Audit of results of operations for infantile pyloric stenosis in a district general hospital. *Arch Dis Child* 1991;**66**: 130–2.

2 Kiely EM. Commentary. *Arch Dis Child* 1991; **66**:132–3.

3 Zeidan B, Wyatt J, Mackersie A, Brereton RJ. Recent results of treatment of infantile pyloric stenosis. *Arch Dis Child* 1988;**63**:1060–4.

4 Jacoby NM. Pyloric stenosis: selective medical and surgical treatment. A survey of 16 years' experience. *Lancet* 1962;i:119–21.

Collodion babies with Gaucher's disease—a further case

Sir,—Lui *et al* reported two neonatal siblings with ichthyosis and Gaucher's disease who died in the first days of life.[1] We wish to report another case.

Case report

The first child of a non-consanguinous white couple was born at appropriate weight for gestational age at 32 weeks' gestation. There was no family history of birth defects, skin disorders, or haematological problems. At birth the baby had moderate ichthyosis with ectropion and some restriction of movement of the digits, presenting as a mild form of the 'collodion baby' phenotype. Hepatosplenomegaly was noted. The ichthyosis improved over the first 10 days, thrombocytopenia developed, and the baby's condition deteriorated with apnoea, suspected infection, and jaundice. Because of the report of Lui *et al*, leucocyte enzyme assays were performed and showed a gross deficiency in the β glucocerebrosidase activity measured with the natural β glucocerebroside substrate (53 pmol/min/mg protein, normal 600–3200) or the artificial 4mu substrate (19 pmol/min/mg protein, normal 60–220). The child died at the age of 3 weeks and postmortem liver histopathology confirmed a diagnosis of Gaucher's disease.

This is the third reported case in the same city in Australia. The family in Lui *et al* came from the western suburbs of Sydney.[1] The families were unrelated. We suspect that this diagnosis may be being overlooked in the differential diagnosis of ichthyosis in the neonatal period.

The reason for the association is by no means certain. Other associations with disorders of lipid metabolism and ichthyosis include X linked ichthyosis with steroid sulphatase deficiency, neutral lipid storage disease, Refsum's disease, and multiple sulphatase deficiency. Alternatively, it was suggested by Lui *et al*, the combination may represent manifestation of a contiguous gene disorder.[1]

A H LIPSON
M ROGERS
A BERRY
The Children's Hospital,
PO Box 34, Camperdown,
Sydney, NSW,
Australia

We thank Dr EF Robertson of Adelaide Children's Hospital for the enzyme studies and Dr C Commens for his comments.

1 Lui K, Commens C, Choong R, Jaworski R. Collodion babies with Gaucher's disease. *Arch Dis Child* 1988;**63**:854–6.

BOOK REVIEWS

The Child Surveillance Handbook. By D M B Hall, P Hill, D Elliman. (Pp 257; £14·95 paperback.) Radcliffe Medical Press, 1990. ISBN 1-870905-66-0.

At last a readable book that paediatricians can recommend for general practitioners, health visitors, and community medical officers undertaking child health surveillance.

The book is divided into two parts 'health promotion', which is further subdivided into primary, secondary, and tertiary prevention, and 'putting the programme into practice' which is split by developmental stages up to school entry. The latter has a very basic 'what to do' and 'how to do it' approach to commonly encountered clinical problems that will suit those new to surveillance.

The child psychiatry input to the assessment and management of common behaviour problems is particularly valuable and will add greatly to the practical value of the book. The flow diagrams and diary suggestions should lead to successful resolution of many of these types of disorder.

No book of this size could claim to be comprehensive, and personally I would have liked a larger section on breast feeding and management of breast feeding related problems, the effects on children of separation and divorce, and more discussion on the primary health care team involvement in health protection. Continuation of the practice established in earlier chapters of suggestions for 'further reading' would also have been useful after the later chapters.

Paediatricians involved with training for surveillance will be encouraged to know that the authors, the Child Growth Foundation, Radcliffe Medical Press, and others are developing a series of training packages to complement this book and covering other aspects of child health care. I look forward to reviewing them.

SIMON LENTON
Community paediatrician

Handbook of Paediatric Dermatology. 2nd Ed. By John Harper. (Pp 228; £29·50 hardback.) Butterworth-Heinemann, 1990. ISBN 0-750-61027-1.

'Harper's handbook' will now be even more popular. The winning combination being quality colour photographs with equally clear and succinct text.

This new edition has up to date illustrations and accounts of child abuse, prenatal diagnosis, Lyme disease, Kawasaki's disease, and a new chapter on tropical dermatoses. The references and appendices have been updated throughout, including a useful list of British and American patient support groups.

Notably, in the five years since the first edition, the incidence of infantile eczema has been changed from 1–3% to 5–10%. In line with present confusion, the advice that breast feeding 'has been shown to decrease the risk of eczema' has been changed to 'breast feeding should be encouraged but there is no evidence that this reduces the risk of eczema'.

As a paediatrician in training I felt this book gave me no guidance on the profound effects of skin disease on growing children, and how to handle them. Eczema treatment is directed to the skin rather than to the child. Until we can cure the chronic skin diseases we must surely be prepared to treat the resulting distress.

A recent rival (Verbov's *Essential Paediatric Dermatology*) provides a more personal anecdotal approach. Equally beautifully illustrated, this book contains many useful tips such as: how to discourage itchy children from scratching, and lice in eyelashes are usually pubic so check the parents. However in achieving this Verbov's book is necessarily more verbose and less comprehensive.

'Harper's handbook' will remain essential to students taking final MB, DCH, and especially membership. Its clarity and brevity make it pleasurable reading cover to cover. Moreover the efficient index and organisation will make it the chosen reference companion to all paediatricians, dermatologists, and general practitioners caring for children with skin disorders.

BENJAMIN JACOBS
Paediatric registrar

European Journal of
Pediatrics
Incorporating
Acta Paediatrica Belgica
and
Helvetica Paediatrica Acta

Volume 150 No. 4 1991

Jürgen Spranger: on the occasion of his 60th birthday 219

Review

Balloon occlusion aortography
T. Ino, S. Shimazaki, K. Nishimoto, K. Akimoto, M. Iwahara, K. Yabuta, M. Watanabe, A. Tanaka, Y. Hosoda
220

Hematology/Oncology

Diffuse infantile haemangiomatosis: clinicopathological features and management problems in five fatal cases
R. W. Byard, P. E. Burrows, T. Izakawa, M. M. Silver 224

Mega-dose intravenous methylprednisone for the treatment of onyalai: a case report
Ş. Özsoylu, G. Ertürk 228

Immunology/Allergology

Lmyhocyte subsets in whole blood and isolated mononuclear leucocytes of healthy infants and children
N. Remy, M. Oberreit, G. Thoenes, U. Wahn 230

IgG2 deficiency in children with human immunodeficiency virus infection
P. Bartmann, I. Grosch-Wörner, V. Wahn, B. H. Belohradsky 234

Effects of short-term administration of human chorionic gonadotropin on immune functions in cryptorchid children
M. Maghnie, A. Valtorta, A. Moretta, D. Larizza, M. A. Girani, F. Severi 238

Severe pulmonary vascular occlusive disease following bone marrow transplantation in Omenn syndrome
C. Brückmann, W. Lindner, R. Roos, W. Permanetter, R. J. Haas, S. G. Haworth, B. H. Belohradsky 242

Medical genetics

New observations on midline defects: Coincidence of anophthalmos, microphthalmos and cryptophthalmos with hypothalamic disorders
J. R. Bierich, M. Christie, J. J. Heinrich, A. S. Martinez 246

The Floating-Harbor syndrome
F. Majewski, H.-G. Lenard 250

Cystic fibrosis and Helicobacter pylori gastritis, megaloblastic anaemia, subnormal mentality and minor anomalies in two siblings: a new syndrome?
M. M. Lubani, Q. A. Al-Saleh, A. S. Teebi, A. Moosa, M. H. Kalaoui 253

Prenatal deletion detection in a sporadic case of Duchenne muscular dystrophy without genotype information from the affected individual
F. Peinemann, M. Wagner, U. Franke, M. Kulle, J. Reiss 256

Metabolic diseases

Renal tubular dysfunction in methylmalonic acidaemia
C. T. D'Angio, M. J. Dillon, J. V. Leonard
259

Cystic fibrosis presenting with recurrent vomiting and metabolic alkalosis
P. M. Mathew, J. A. Hamdan, H. Nazer
264

Neonatology

Breast mild jaundice: natural history, familial incidence and late neurodevelopmental outcome of the infant
E. Grunebaum, J. Amir, P. Merlob, M. Mimouni, I. Varsano 267

First day serum creatine kinase BB isoenzyme in high-risk infants
R. A. Primhak, E. Simmonds 271

Clinical usefulness of high intensity green light phototherapy in the treatment of neonatal jaundice
M. Amato, D. Inaebnit 274

Early onset neonatal sepsis with Campylobacter jejuni: a case report
R. Krishnaswamy, P. Sasidharan, A. Rejjal, Y. Abu Osba 277

Nephrology

Haemolytic uraemic syndrome in the defined population of Northeast of Scotland
I. A. Abu-Arafeh, P. J. Smail, G. G. Youngson, I. A. Auchterlonie 279

Neuropediatrics

Brain abscess in childhood – long-term experiences
C. Aebi, F. Kaufmann, U. B. Schaad 282

Low arylsulphatase A activity and choreoathetotic syndrome in three siblings: differentiation of pseudodeficiency from metachromatic leukodystrophy
J. Kappler, R. W. E. Watts, E. Conzelmann, D. A. Gibbs, P. Propping, V. Gieselmann
287

Letter to the editors

The first prenatal diagnosis of dihydropyrimidine dehydrogenase deficiency
C. Jakobs, F. Stellaard, L. M. E. Smit, J. M. G. van Vugt, M. Duran, R. Berger, P. Rovers 291

Abstracts

27th Workshop for Pediatric Research held at the Kinderklinik of the Georg-August-University Göttingen, 28 February–1 March 1991 292

Indexed in *Current Contents*

Springer International

Subscription information

Volume 149 (12 issues) will appear in 1990. Information about obtaining back volumes and microform editions available upon request.

North America. Annual subscription rate: approx. US $ 868.00 (single issue price approx. $ 87.00), including carriage charges. Subscriptions are entered with prepayment only.

Orders should be addressed to:
Springer-Verlag New York Inc.
Service Center Secaucus
44 Hartz Way
Secaucus, NJ 07094, USA
Tel. (201) 348-4033
Telex 023125994
FAX (201) 348-4505

All other countries. Annual subscription rate: DM 1532.00 plus carriage charges; Federal Republic of Germany: DM 20.54 incl. value added tax; all other countries: DM 39.00 except for the following countries to which SAL delivery (Surface Airmail Lifted) is mandatory: Japan DM 103.80, India DM 75.00, Australia/New Zealand DM 119.40. Airmail delivery to all other countries is available upon request. Volume price: DM 1532.00, single issue price: DM 153.20 plus carriage charges. Subscriptions can either be placed via a bookdealer or sent directly to:

Springer-Verlag
Heidelberger Platz 3, D-1000 Berlin 33
Tel. (0)30/8207-0, Telex 183319
FAX (0)30/8214091

“Days to remember … *all my life*”

[redacted]

JUNE 1991 VOL 66 NO 6

Dec 12 9

UCM

ARCHIVES OF DISEASE IN CHILDHOOD

[redacted]

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Editors: Bernard Valman, Malcolm Chiswick
Associate Editors: Derek Johnston, Michael Silverman, Brian Wharton
Statistical Adviser: Michael Healy
Technical Editor: Sue Heels
Editorial Assistant: Jacinta Marshall

EDITORIAL COMMITTEE

F Cockburn
T J David
M J Dillon
M E Garralda
H L Halliday
I M Hann
I A Hughes
J W Keeling
C R Kennedy
S W Lenton
J K Lloyd
H Marcovitch
N McIntosh
P J Milla
L Polnay
P Raine
P T Rudd
J F N Taylor
R M Winter
J E Wraith
Editor, *BMJ*

Published by the British Medical Association, Tavistock Square, London WC1H 9JR and printed in England by The Devonshire Press Ltd, Torquay.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0003–9888

NOTES TO CONTRIBUTORS Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

NOTICE TO ADVERTISERS Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *Archives of Disease in Childhood* is published monthly. The annual subscription rates are £127 inland and £140 overseas (USA $208). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All inquiries however must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All inquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

The British Paediatric Association is a registered charity.

COPYRIGHT © 1991 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

[redacted]

Making sure Ventolin gets through to the younger generation
VENTODISKS
8
7
1
6
2
5
4
3

VENTODISKS

(Salbutamol BP)

Ventodisks (Salbutamol BP). **Abridged Prescribing Information** (Please refer to full data sheet before prescribing.) **Uses**: Treatment and prophylaxis of acute and chronic bronchospasm. **Dosage and administration**: *Adults:* 400 micrograms as single dose or three to four times daily. *Children:* 200 micrograms as single dose or three to four times daily. **Contra-indications**: Threatened abortion during first or second trimester. Hypersensitivity. **Precautions**: If previously effective dose lasts less than three hours, seek medical advice. Caution in patients with thyrotoxicosis. Avoid use with non-selective beta-blockers. Hypokalaemia may occur, particularly in acute severe asthma. It may be potentiated by xanthine derivatives, steroids, diuretics and hypoxia. Serum potassium levels should be monitored in such situations. *Pregnancy:* Avoid unnecessary use during early pregnancy. Only consider if expected benefit outweighs possible risks. *Lactation:* Salbutamol likely to be secreted in breast milk. Effect on neonate unknown. Balance risks against benefits. **Side effects:** Mild tremor, headache occur rarely. Very rarely — transient muscle cramps hypersensitivity reactions. Potentially serious hypokalaemia may result from β_2-agonist therapy. Paradoxical bronchospasm could occur – substitute alternative therapy. **Presentation and Basic NHS cost**: Pack of 14 Ventodisks each containing 8 x 200 micrograms Salbutamol BP (as sulphate) — light blue or 8 x 400 micrograms Salbutamol (as sulphate) — dark blue, together with a Ventolin Diskhaler. For inhalation. £7·11 and £12·02. Refill pack of 14 x 8 Ventodisks only. 200 micrograms, £6·54; 400 microgram £11·45. **Product licence numbers:** Ventodisks 200 micrograms 0045/0134, Ventodisks 400 micrograms 0045/0135.

ALLEN & HANBURYS

Further information is available on request from: Allen & Hanburys Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT
Ventodisks should only be used with a Ventolin Diskhaler. Diskhaler, Ventodisks and Ventolin are trade marks

Archives of Disease in Childhood 1991; 66: 669–671

ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Monitoring TSH concentrations during treatment for congenital hypothyroidism

Treatment of a child with congenital hypothyroidism should be one of the most straightforward and rewarding experiences in paediatrics. As a result of neonatal screening and early diagnosis the prognosis for mental development is greatly improved, treatment itself is simple and inexpensive, and biochemical tests to monitor therapy are widely available. However, most paediaticians will have encountered cases during treatment in which the laboratory results are difficult to interpret as the plasma thyroid stimulating hormone (TSH) concentration is abnormal even though plasma thyroxine—measured either as total thyroxine or free thyroxine—is normal. Such cases are relatively common, particularly during early infancy. For example, 34% of the children with congenital hypothyroidism reported by Hulse *et al* had raised TSH concentrations at the age of 1 year.[1] Similarly, Abusrewil *et al* found TSH values above 10 mU/l in 38% of cases tested between 5 and 11 months,[2] and Germak and Foley found high TSH concentrations at 1 year in 23% of their patients with thyroid dysgenesis[3]; interestingly, their cases with dyshormonogenesis all had normal TSH values.[3]

Are these discrepancies between TSH and thyroxine concentrations important and what do they mean?

Measurement of thyroxine and TSH reflect slightly different aspects of thyroid status, the former indicating thyroid activity (or replacement treatment with thyroxine), and the latter gives information on the biological effect of circulating thyroid hormone. The reciprocal relationship between the two is well known but the mechanisms behind it are still incompletely understood. However, it seems clear that the set point which defines the concentration of plasma thyroxine at which TSH secretion is normal varies between individual subjects and also changes with age. This set point is associated with high plasma thyroxine values during the first months of life, followed by a progressive decline during childhood.[4] Change in the set point also occurs as a result of illness, particularly thyroid disease; for example, TSH secretion remains suppressed for some time after hyperthyroidism has been relieved.[5] The variation in set point during early infancy and delay in establishing a new threshold when plasma thyroxine returns to normal probably account for most of the discrepancies between plasma thyroxine and TSH results encountered during treatment of congenital hypothyroidism.

It has long been known that in adults with hypothyroidism plasma thyroxine must be maintained in the upper normal range to suppress TSH.[6] This is also the case in congenital hypothyroidism,[4] and many studies have shown that raised plasma TSH concentrations during treatment are almost invariably associated with plasma thyroxine concentrations in the mid to lower part of the normal range.[1,2,7,8] In a few cases, raised TSH concentrations have been associated with thyroxine concentrations well above normal and this has been attributed to delay in maturation of the pituitary-thyroid axis.[9] The children with raised TSH concentrations have generally been receiving a relatively low dose of thyroxine, and the optimum dose which will keep TSH within normal has been estimated at 100-105 µg/m^2,[7,10] with a high dose relative to body weight (8 to 14 µg/kg) in early infancy.[1,3]

Delay in reaching a new set point after a change in plasma thyroxine concentration can also result in discrepancies between plasma thyroxine and TSH. This is commonly seen during the first weeks of treatment when plasma thyroxine returns to normal much more quickly than TSH.[3] Delay in reaching a new threshold may also cause discrepant results if compliance with treatment is poor. Regular administration of thyroxine shortly before an outpatient visit will largely correct plasma thyroxine without completely suppressing TSH.

Does it matter if plasma TSH is mildly raised during treatment if the patient appears euthyroid with normal growth and normal mental development? In many cases the answer is probably 'no', particularly if there has been a recent change in dosage of thyroxine or if the plasma thyroxine concentration is close to the upper limit of normal. However, we still do not know whether slight undertreatment has any long term adverse effects, for example on psychological outcome, and ideally plasma TSH should be maintained between 0·1 and 5 mU/l.[3] My own practice is to try to keep plasma TSH as near normal as possible during early infancy but to discount slightly raised values in older children, particularly if growth is normal.

Is there a risk of overdosage if treatment aims to keep TSH within the normal range? The answer to this question must be 'yes' until the new immunoradiometric (IRMA)—or immunofluorometric (IFMA)—assays for TSH are more widely available. These assays are many times more sensitive than the original radioimmunoassays and can identify TSH concentrations that fall below the lower limits of normal.[11] There is some evidence that clinical problems such as poor concentration or restlessness may be associated with relatively minor degrees of overtreatment[8] and the new assay methodology will allow further evaluation of this aspect of congenital hypothyroidism.

D B GRANT

Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH

1 Hulse JA, Grant DB, Jackson D, Clayton BE. Growth, development, and reassessment of hypothyroid infants diagnosed by screening. *BMJ* 1982; **284**:1435–7.
2 Abusrewil SSA, Tyfield L, Savage DCL. Serum thyroxine and thyroid stimulating hormone concentrations after treatment of congenital hypothyroidism. *Arch Dis Child* 1988;**63**:1368–71.
3 Germak JA, Foley TP. Longitudinal assessment of l-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1990;**117**:211–9.
4 Sato T, Suzuki Y, Taketani T, Ishiguru K, Nakajima H. Age related change in pituitary threshold for TSH release during thyroxine replacement therapy for cretinism. *J Clin Endocrinol Metab* 1977;**44**:553–9.
5 Toft AD, Irvine WJ, Hunter WM, Ratcliffe JG, Seth J. Anomalous plasma TSH levels in patients developing hypothyroidism in the early months after I131 therapy for thyrotoxicosis. *J Clin Endocrinol Metab* 1974;**39**:607–9.
6 Reichlin S, Utiger RD. Regulation of the pituitary-thyroid axis in man: relationship of TSH concentration and concentration of free and total thyroxine in plasma. *J Clin Endocrinol Metab* 1967;**27**:251–5.
7 Rezvani I, DiGeorge AM. Reassessment of the dialy dose of oral thyroxine for replacement therapy in hypothyroid children. *J Pediatr* 1977;**90**:291–7.
8 Frost GJ, Parkin JM. Management of patients with congenital hypothyroidism. *BMJ* 1985;**290**:1485–9.
9 Schultz RM, Glassman MS, MacGillvray MH. Elevated threshold for thyrotropin suppression in congenital hypothyroidism. *Am J Dis Child* 1980;**134**: 19–20.
10 Hodges S, O'Malley BP, Northover BN, Woods KL, Swift PGF. Reappraisal of thyroxine treatment in primary hypothyroidism. *Arch Dis Child* 1990;**65**: 1129–32.
11 Nicoloff JT, Spencer CA. The use and misuse of sensitive thyrotropin assays. *J Clin Endocrinol Metab* 1990;**71**:553–8.

Pitfalls in the diagnosis of congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a rare anomaly occurring in one in 3600 live births. If affected fetuses are taken into account the incidence is increased to one in 2200.[1] An increasing proportion of these cases are being diagnosed as a result of routine antenatal scanning. There remain a significant number of affected patients who present for the first time in the neonatal period and a further group presenting as older infants or children.

Neonatal diagnosis and pitfalls

The classical presentation of a neonate in respiratory distress, with a scaphoid abdomen, apparent dextrocardia, and multiple air and fluid filled bowel loops in the left hemithorax on chest radiography presents no diagnostic difficulty. Occasionally the chest radiograph is taken before the passage of swallowed air into the herniated intestine and will thus demonstrate a radio-opaque hemithorax. The absence of intestinal gas in the abdomen should provide the diagnostic clue in these cases.[2] In all cases the abdomen should be included on the radiograph if CDH is suspected. The existence of a previously normal chest radiograph does not preclude the diagnosis.[3] The defect in the diaphragm may be plugged by a solid abdominal viscus, for example, liver, spleen, or omentum.[4] The delayed appearance may on some occasions be related to initially raised intrathoracic pressure which when lowered allows the abdominal viscera to enter into the affected hemithorax.[5]

There is a further group of neonates with delayed appearance of right diaphragmatic hernia associated with group B streptococcal infection, and neonates with relapsing streptococcal infection should have this diagnosis positively excluded.[6 7] Right sided hernias may present as a pleural effusion, the obstructed hepatic venous outflow from herniated liver causing vascular congestion and transudation from the liver surface.[4 8] The effusion may compress the adjacent lung resulting in atelectasis which may mimic primary pulmonary pathology, or may prevent identification of either the herniated liver or the diaphragm itself. Ultrasound should establish the diagnosis in these cases. Paraoesophageal and oesophageal hiatal hernias are generally associated with vomiting rather than respiratory embarrassment. Large paraoesophageal hernias are usually identified in the posterior right cardiophrenic region and easily confirmed on barium studies. The differentiation of cystic adenomatoid malformation, congenital lobar emphysema, and CDH may present diagnostic difficulty as they may all present with respiratory distress at or shortly after birth.[9–11] If the chest radiograph is taken too early the affected lung in cystic adenomatoid malformation and congenital lobar emphysema may be fluid filled. There are several diagnostic pointers which assist in establishing the correct diagnosis. The presence of normal intestinal gas shadows within the abdominal cavity should raise doubts about the diagnosis of CDH. The position of the tip of the nasogastric tube may be helpful when the stomach lies above the diaphragm, and in these instances it may be a prognostic indicator, as the presence of an intrathoracic stomach has been equated with an adverse prognosis.[12] On rare occasions air or contrast may be instilled via the nasogastric tube to determine the position of the stomach and small intestine. Ultrasound may prove helpful and may demonstrate the diaphragmatic defect with bowel or, if on the right, liver passing through. Congenital lobar emphysema usually involves the upper lobes and the chest radiograph most commonly shows hyperlucency rather than an appearance similar to bowel gas shadows.[9] There have been reports of the other congenital bronchopulmonary malformations being misdiagnosed as CDH, but these reports stress the importance of careful interpretation of the chest and abdominal radiographs, and if necessary, the use of ultrasound.[13 14]

Eventration is more common on the right, usually contains liver, and is most easily diagnosed by ultrasound. Occasionally the fine distinction between a partition containing a few strands of muscle, that is, a diaphragmatic eventration, and a peritoneal sac without striated muscle, that is, a hernia, may prove difficult even at surgery, but in such cases the distinction is unimportant.[15]

Staphylococcal pneumonia that has progressed to produce pneumatocoeles may have an appearance on chest radiography that on first inspection mimics CDH.[15] Staphylococcal pneumonia may affect either lung and the bowel gas pattern will be normal. The clinical presentation will be different and the presence of earlier films should prove helpful.

Urgent surgery for CDH has been superceded by a period of preoperative resuscitation and stabilisation which may extend over several days.[16] The rapid presumptive diagnosis of CDH remains essential for the correct management to be instituted. The period of preoperative stabilisation allows ample time for the definitive diagnosis to be established by the full range of necessary radiological investigations if required.

Diagnosis and pitfalls in the older child

The initial impression that CDH is rare beyond the neonatal period has how been revised. The reported incidence ranges from 5 to 25% of patients with CDH.[17 18] The wide variety of symptoms and signs in the older age group compound the diagnostic difficulty. Recurrent chest infections, acute respiratory distress, recurrent vomiting, diarrhoea or constipation, and failure to thrive are some of the reported presenting symptoms.[17 18] The clinical signs may be equally non-specific. The hernias may be intermittent or only demonstrable in Trendelenberg's position.[19 20] Thus the presence of a normal or previously normal chest radiograph does not exclude the diagnosis. At least 22 documented cases of left posterolateral hernia have been reported in the English literature in patients with previously normal chest radiographs.[18] The size of the hernia bears no relation to the severity of the symptoms. The most frequent misdiagnosis after chest radiography appears to be pneumonia, although other diagnoses such as pneumothorax, cystic lung bullae, and gastric volvulus have been reported.[18 21]

Careful interpretation of the chest and abdominal radiographs at presentation will, as in the neonatal group, usually lead to the correct diagnosis. The presence of haustral markings or valvulae conniventes will help identify bowel, although these may be difficult to appreciate on a supine film and an erect film may be required. The passage of a nasogastric tube may enable the correct diagnosis to be made in left sided hernia when the stomach lies in the chest. Other imaging modalities which may be helpful include a barium meal and follow through or barium enema as most hernias in this group will contain some part of the gastrointestinal tract. Recent reports suggest that Morgagni hernia more frequently contain bowel than was previously recognised.[18] Although Morgagni hernia are more likely to present as a chance finding, the presence of a hollow viscus increases the likelihood of symptoms. As in neonates, right sided hernias frequently contain liver and in the older child may be asymptomatic. Ultrasound may demonstrate the diaphragmatic defect, if required.[22] In both left and right sided herniation intestinal obstruction or strangulation is a well reported occurrence.[23 24]

In both groups the correct diagnosis is nearly always apparent on close inspection of the presentation radiographs. The most likely diagnostic error is cystic adenomatoid malformation in the neonatal group and pneumonia in the older group. If further investigation is required the passage of a nasograstric tube may prove helpful in both groups. If the diagnosis is still not clear an ultrasound in the neonatal group and a barium study in the late presentation group will establish the diagnosis in most instances.

F GLEESON
Department of Radiology
L SPITZ
Department of Surgery

Hospital for Sick Children,
Great Ormond Street,
London WC1N 1EH

1 Butler N, Claireaux AE. Congenital diaphragmatic hernia as a cause of perinatal mortality. *Lancet* 1962;i:659–63.
2 Singleton EB, Wagner ML, Dutton RV. *Radiologic atlas of pulmonary abnormalities in children*. Philadelphia: WB Saunders, 1988.
3 Fauré C, Sauvegrain J, Bomsel F. Right-sided congenital diaphragmatic hernia with delayed radiological manifestations. *Ann Radiol (Paris)* 1971; **14**:305–13.
4 Blank E, Campbell JR. Congenital posterolateral defect in the right side of the diaphragm. *Pediatrics* 1976;**5**:807–10.
5 McClead RE, Graham M, Fletcher BD. Postnatal appearance of diaphragmatic hernia. *Am J Dis Child* 1978;**132**:1137–8.
6 Ashcraft KW, Holder TM, Amoury RA, *et al*. Diagnosis and treatment of right Bochdalek hernia associated with group B streptococcal pneumonia and sepsis in the neonate. *J Pedtr Surg* 1983;**18**:480–5.
7 McCarten KM, Rosenberg HK, Borden S, Mandell GA. Delayed appearance of right diaphragmatic hernia associated with group B streptococcal infection in neonates. *Pediatr Radiol* 1981;**139**:385–9.
8 Chilton HW, Chang JHT, Jones MD, Brooks JG. Right-sided congenital diaphragmatic hernia presenting as pleural effusions in the newborn: dangers and pitfalls. *Arch Dis Child* 1978;**53**:600–3.
9 Heji HA, Ekkelkamp S, Vos A. Diagnosis of congenital cystic adenomatoid malformation of the lung in newborn infants and children. *Thorax* 1990;**45**: 122–5.
10 Belanger R, Fleche LR, Pickard JL. Congenital cystic adenomatoid malformation of the lung. *Thorax* 1964;**19**:1–11.
11 Nishibayashi SW, Andrassy RJ, Wooley MW. Congenital cystic adenomatoid malformation: a 30-year experience. *J Pediatr Surg* 1981;**16**:704–6.
12 Goodfellow T, Hyde I, Burge DM, Freeman NV. Congenital diaphragmatic hernia: the prognostic significance of the site of the stomach. *Br J Radiol* 1987;**60**:993–5.
13 Muayed R, Azmy AF, Fyfe AHB, Cochran W. Congenital cystic adenomatoid malformation of the lung. Potential diagnostic pitfall. *Surgery In Infancy And Childhood* 1986;**41**:107–8.
14 Bailey PV, Tracy T, Connors RH, deMello D, Lewis JE, Weber TR. Congenital bronchopulmonary malformations. *J Thorac Cardiovasc Surg* 1990;**99**:597–603.
15 Bonham Carter RE, Waterston DJ, Aberdeen E. Hernia and eventration of the diaphragm in childhood. *Lancet* 1962;i:656–9.
16 Tibboel D, Bos AP, Pattenier JW, Hazebroek FWJ, Mader N, Molenaar JC. Pre-operative stabilisation with delayed repair in congenital diaphragmatic hernia. *Z Kinderchir* 1989;**44**:139–44.
17 Newman BM, Afshani E, Karp MP, Jewett TC, Cooney DR. Presentation of congenital diaphragmatic hernia past the neonatal period. *Arch Surg* 1986; **121**:813–6.
18 Berman L, Stringer DA, Ein S, Shandling B. Childhood diaphragmatic hernias presenting after the neonatal period. *Clin Radiol* 1988;**39**:237–44.
19 Hight DW, Hixson SD, Reed JO, Watts FB, Hertzler JH. Intermittent diaphragmatic hernia of Bochdalek: report of a case and literature review. *Pediatrics* 1982;**69**:601–4.
20 Booker PD, Meerstadt PWD, Bush GH. Congenital diaphragmatic hernia in the older child. *Arch dis Child* 1981;**56**:253–7.
21 Berman L, Stringer D, Ein SH, Shandling B. The late presenting paediatric Bochdalek hernia. *J Pediatr Surg* 1988;**23**:735–9.
22 Merten DF, Bowie JD, Kirks DR, Grossman H. Anteromedial diaphragmatic defects in infancy: current approaches to diagnostic imaging. *Pediatr Radiol* 1982;**142**:361–5.
23 Wooley MM. Delayed appearance of a left posterolateral diaphragmatic hernia resulting in significant small bowel necrosis. *J Pediatr Surg* 1977;**12**:673–4.
24 Campbell DN, Lilly JR. The clinical spectrum of right Bochdalek's hernia. *Arch Surg* 1982;**117**:341–4.

Archives of Disease in Childhood 1991; **66:** 672–675.

ORIGINAL ARTICLES

Hypoxaemia after nebulised salbutamol in wheezy infants: the importance of aerosol acidity

J Seidenberg, Y Mir, H von der Hardt

Abstract

The effect of nebulised iso-osmolar, preservative free, but acidic salbutamol solution was studied in 34 acutely wheezing infants aged 1–17 months. Transcutaneous oxygen pressure ($TcPo_2$) and oxygen saturation (So_2) fell significantly during the first five minutes after nebulisation with further deterioration at 15–20 minutes. Ten of these infants were followed up for another two hours and showed slight improvement. Even after the second hour $TcPo_2$ had not reached baseline values. Three months later the response to salbutamol and a placebo of equal acidity (pH 3·9) was studied in 11 infants from the same group, now free of symptoms. Lung function tests were included and showed no significant changes in specific conductance and volume corrected maximum expiratory flows ($\dot{V}max$ at functional residual capacity/thoracic gas volume). However, hypoxaemia occurred after the acidic placebo with a significant drop of $TcPo_2$ (mean 0·9 kPa); So_2 decreased similarily but this did not reach significance. After salbutamol there was a further significant deterioration of mean $TcPo_2$ (1·4 kPa) and of So_2. These results show that beside a possible pharmacological effect of salbutamol the acidity of the aerosol also induces hypoxaemia in infants.

Nebulised salbutamol has been shown to cause hypoxaemia in acutely wheezy infants.[1] Similarly, several lung function parameters of wheezy infants were found to deteriorate after nebulisation of salbutamol,[2–4] but their relation to hypoxaemia has not been proved. The mechanisms of hypoxaemia after inhalation of salbutamol are still unclear. An increase of ventilation-perfusion mismatch could be caused by raised pulmonary perfusion[5] as well as reduced airway smooth muscle tone leading to higher airway compression during forced expiration.[2 3] Also the physical properties of the aerosol including acidity and osmolarity[4] or the content of preservative[6] may be responsible for the observed negative effects. Furthermore hypoxaemia could be explained by a rise in oxygen consumption, which may be induced by salbutamol[7] or just by the sedation (chloral hydrate),[8] which is often used to perform the lung function tests.

The clinically important observation of hypoxaemia after nebulisation of salbutamol has so far been made in only five wheezy infants, who all were sedated with chloral hydrate.[1] The observation period was no longer than 20 minutes and oxygen pressure did not return to baseline during that time period. The placebo used was physiological saline; the salbutamol solution however was acidic.[1 9]

We therefore performed two test series to obtain further information. In both tests transcutaneous oxygen pressure ($TcPo_2$) and saturation (So_2) were measured after nebulisation of a preservative free and iso-osmolar salbutamol solution. In the first test acutely wheezing infants were studied without sedation over a period of 2·5 hours. From these, some infants could be re-examined when free of symptoms with additional lung function tests before and after salbutamol and placebo of equal acidity.

Patients and methods

For the first test, 34 acutely wheezy infants aged 1–17 months (mean age 6·6 months) were studied shortly after admission to hospital. Readings of $TcPo_2$ (Kontron Cutan 820) were taken after calibration in air by placing the heated electrode (44°C) on the upper thorax of the infants and allowing a stabilisation period of 15–20 minutes. Heart rate and So_2 (Dräger Nellcor 100) were recorded simultaneously, and special care was taken to discard artefacts. All the readings were only taken when the infants were asleep or lying quietly without body movements.

The patients were not sedated and had not received any bronchodilator during the previous eight hours. An iso-osmolar solution containing 2·5 mg of preservative free salbutamol (2·5 ml Salbutamol 5 Riker Infusionskonzentrat, 290 mosm/kg, pH 3·9) were given by a Turret nebuliser (Medic Aid) driven by compressed air at 6 l/minute for about five minutes. $TcPo_2$ and So_2 were observed continuously, values were collected at minute intervals, and the mean values for the five minutes before and after nebulisation were analysed as well as the mean values from the 15th to 20th minute.

After measurements had been obtained from 15 patients, we decided to extend the observation period and 10 patients could be follow up to 2·5 hours. The means from 60–80 minutes and 120–140 minutes after nebulisation were recorded.

Informed consent was obtained from parents of 11/34 infants to participate in a second test about three months later when the infants were without clinical symptoms and free of infection. Their mean age then was 9·5 months (range 6–14 months). They received 80–100 mg/kg chloral hydrate orally. When asleep, baseline values for airway resistance and thoracic gas

Department of Paediatric Pneumology, Kinderklinik der Medizinischen Hochschule, 3000 Hannover 61, Federal Republic of Germany
J Seidenberg
Y Mir
H von der Hardt

Correspondence to:
Dr J Seidenberg,
Abteilung Pädiatrische Pneumologie,
Kinderklinik der Medizinischen Hochschule Hannover,
3000 Hannover 61,
Federal Republic of Germany.

Accepted 30 January 1991

volume (TGV) were measured in a volume constant baby body plethysmograph (Fenyves and Gut) under body temperature, pressure, and saturation (BTPS) conditions. Maximum flow at functional residual capacity (FRC) (Vmax FRC) was obtained by the chest compression technique described elsewhere.[10 11] $TcPo_2$, So_2 and heart rate were recorded as described above. An aliquot of 2·5 ml of acidic placebo (physiological saline, titrated to pH 3·9 with hydrochloric acid, osmolarity 280 mosm/kg) was nebulised with the same Turret nebuliser and flow rate for about five minutes. Fifteen to 20 minutes later the infants received the same dose of salbutamol as in the first test. After both nebulisations measurements of $TcPo_2$, So_2 and heart rate were averaged for the first five minutes after nebulisation and lung function tests were repeated.

The Wilcoxon matched paired test for nonparametric data was used to describe significant differences ($p<0·05$). These were similar to results obtained using equivalent *t* tests, therefore values are expressed as mean and SD.

Results

FIRST TEST: ACUTELY WHEEZY INFANTS

Thirty of 34 infants remained undisturbed throughout the test, but four infants fell asleep or woke up so that comparable measurements could not be obtained.

Table 1 Mean (SD) values of oxygen saturation (So_2), transcutaneous oxygen pressure ($TcPo_2$), and heart rate before and up to 20 minutes after salbutamol (n=30)

	Baseline	*0–5 Minutes*	*15–20 Minutes*
So_2 (%)	95 (3·8)	93 (4·6)*	93 (4·5)*
$TcPo_2$ (kPa)	8·2 (1·8)	7·5 (1·9)*	7·2 (1·9)*†
Heart rate (1/min)	131 (18)	135 (18)*	139 (17)*†

*Significantly different ($p<0·05$) to baseline value; †significantly different ($p<0·05$) to preceding value.

Baseline readings for $TcPo_2$ and So_2 are listed in table 1. After salbutamol a significant fall occurred for $TcPo_2$ and So_2 within the first five minutes ($p<0·001$). Further deterioration was observed after 15–20 minutes. Compared with baseline values, the mean $TcPo_2$ had decreased from 8·2 kPa to 7·2 kPa and So_2 from 95% to 93%. Individual changes are shown in fig 1.

The long term follow up in 10 patients showed improvement after one and two hours, $TcPo_2$ still remaining significantly below the baseline values (7·1 kPa, $p<0·006$ and 7·4 kPa, $p<0·047$) (table 2, fig 2). So_2 had normalised after the second hour except in five patients with values of more than 1% below the baseline value. Mean heart rate rose significantly after salbutamol from 131/minute to a maximum of 139/minute 20 minutes after nebulisation. After one hour heart rate was still raised ($p<0·007$).

SECOND TEST: INFANTS FREE OF SYMPTOMS

Three of 11 infants woke up after the measurements taken after the placebo. Only complete data sets were compared: for $TcPo_2$ and So_2 this was obtained in eight infants; for airway mechanics in six infants only.

Baseline readings for $TcPo_2$ (10·4 kPa) and So_2 (98%) had now reached normal range in most patients (table 3). After nebulisation of the acidic placebo, values for $TcPo_2$ fell significantly to 9·5 kPa ($p<0·012$) within the first five minutes and recovered to 10·0 kPa within the 15th to 20th minute after nebulisation ($p=0·164$, fig 3). However, $TcPo_2$ was still significantly different from baseline ($p<0·013$). After

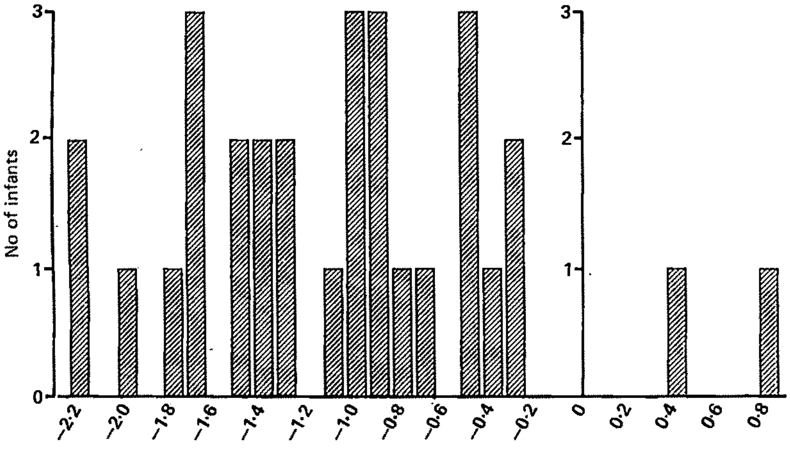


Figure 1 Individual changes in transcutaneous oxygen pressure ($TcPo_2$) 20 minutes after salbutamol (n=30). A fall was observed in 28 and an increase in two infants.

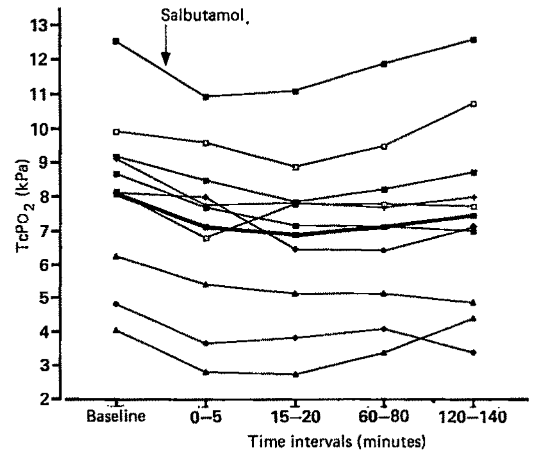


Figure 2 Changes in transcutaneous oxygen pressure ($TcPo_2$) up to 2·5 hours after salbutamol (n=10). The bold line indicates the mean value.

Table 2 Mean (SD) values of oxygen saturation (So_2), transcutaneous oxygen pressure ($TcPo_2$), and heart rate before and up to 2·5 hours after salbutamol (n=10)

	Baseline	*0–5 Minutes*	*15–20 Minutes*	*60–80 Minutes*	*120–140 Minutes*
So_2 (%)	93 (2·7)	91 (4·4)*	91 (4·5)*	92 (3·4)*	92 (3·2)
$TcPo_2$ (kPa)	8·1 (2·4)	7·1 (2·4)*	6·9 (2·4)*	7·1 (2·4)*	7·4 (2·7)*
Heart rate (1/min)	127 (12)	132 (14)*	134 (15)*†	134 (13)*	129 (16)†

*Significantly different ($p<0·05$) to baseline value; †significantly different ($p<0·05$) to preceding value.

Table 3 Mean (SD) values of oxygen saturation (So$_2$), transcutaneous oxygen pressure (TcPo$_2$), heart rate, and lung function (% predicted) at baseline, after acidic placebo, and after salbutamol

	No of patients	*Baseline*	*After placebo: early*	*After placebo: late*	*After salbutamol*
So$_2$ (%)	8	98 (1·1)	97 (2·2)	98 (1·3)	96 (2·0)*†
TcPo$_2$ (kPa)	8	10·4 (1·3)	9·5 (1·9)*	10·0 (1·4)*	8·6 (1·8)*†‡
Heart rate (1/min)	8	122 (10·9)	125 (8·2)	122 (10·8)	141 (10·8)*†‡
$\dot{V}$max FRC (%)	6	48 (18)	42 (16)	—	50 (22)
Airway resistance (%)	6	95 (28)	114 (23)	—	119 (27)
TGV (%)	6	147 (20)	130 (18)*	—	132 (21)
Specific conductance (1/second/kPa)	6	0·16 (0·05)	0·14 (0·05)	—	0·13 (0·04)
Vmax FRC/TGV (1/second)	6	0·41 (0·18)	0·40 (0·18)	—	0·47 (0·22)

*Significantly different (p<0·05) to baseline value; †significantly different (p<0·05) to after placebo, late; ‡significantly different (p<0·05) to after placebo, early.
FRC, functional residual capacity; TGV, thoracic gas volume.

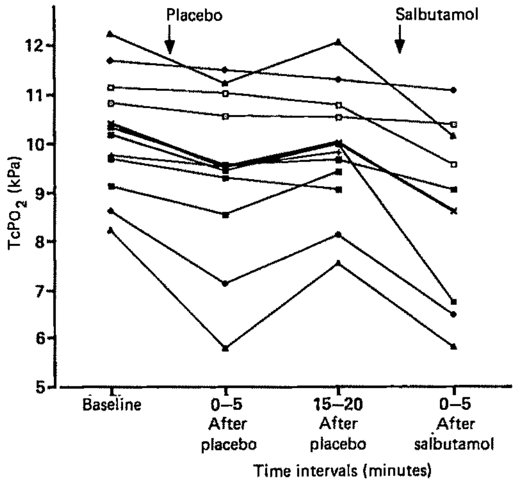


Figure 3 Changes in transcutaneous oxygen pressure (TcPo$_2$) after acidic placebo (n=11) and after salbutamol (n=8). The bold line indicates the mean value.

salbutamol TcPo$_2$ decreased even further to 8·6 kPa, significantly different from baseline values (p<0·012) and from both readings after placebo (p<0·018 and p<0·012). Smaller changes could be observed with So$_2$ (table 3), the only significant difference occurring between before and after salbutamol (p<0·012).

Baseline lung function expressed as percentage of predicted values[10 12] were normal for airway resistance (95%), raised for TGV (147%) and decreased for Vmax FRC (48%), indicating a persisting small airway obstruction; therefore specific conductance (0·16/second/kPa) and VmaxFRC/TGV (0·41/second) were diminished (table 3).

After the acidic placebo airway resistance increased to 114% predicted (p=0·141), TGV decreased to 130% predicted (p<0·028), and specific conductance remained little changed (0·14/second/kPa, p=0·465). VmaxFRC decreased slightly to 42% (p<0·044), but Vmax FRC/TGV remained unchanged (0·40/second, p=0·465).

Lung function after salbutamol was not significantly different to baseline and after placebo values.

Discussion

In the present study on 34 infants we have confirmed the clinically important observation of Prendiville *et al*, that is, that hypoxaemia occurs after nebulisation of salbutamol in wheezy infants.[1] This is not only a transient effect, as we have shown persistence of low values for oxygen pressure up to two hours thereafter. Our patients were not sedated. We also used an iso-osmolar solution, and although an increase in osmolarity during nebulisation has been described,[4] neither bronchoconstriction nor hypoxaemia[1] has been shown after physiological saline. Our solution did not contain preservatives also known to evoke bronchoconstriction.[6 13]

The salbutamol solution we used, however, was acidic. For the lung function tests we therefore decided to use a placebo of equal acidity, which to our knowledge has not been reported so far. Citric acid has been nebulised to dogs inducing airway obstruction with two mechanisms being suggested by the authors: reflex bronchoconstriction after a nebulisation period of two minutes and a mediator induced bronchoconstriction after nebulisation for five minutes.[14] Swallowing an acidic solution may also lead to airway obstruction,[15] and as in nebulisation a considerable amount of aerosol is swallowed this too has to be taken into account. There are also some reports that in adults bronchoconstriction may occur after inhalation of various acidic aerosols.[16–18]

In infants O'Callaghan *et al* have observed deterioration of specific conductance after nebulisation of a preservative free, iso-osmolar but acidic (pH 3·6) solution of ipratropium bromide.[19] This effect was short lived—lasting for about 10–15 minutes. Similarly, deterioration of airway resistance, specific conductance,[4] and Vmax FRC[3] has been reported after an acidic salbutamol solution. In the present study we could not find significant deterioration in airway resistance, specific conductance or Vmax FRC/TGV after placebo or salbutamol. A possible explanation may be that we measured lung function between seven and 13 minutes after nebulisation to avoid disturbance of oxygen measurements, so we might have missed an initial reaction of airway mechanics. However, we did notice a significant drop of TcPo$_2$ after nebulisation of the acidic placebo which did not fully recover by 20 minutes.

From these results the question arises whether hypoxaemia after salbutamol could be a preventable side effect not related to the drug itself but to acidity. We did not nebulise a neutral salbutamol solution and therefore cannot answer this question definitively. Although severity and duration of hypoxaemia were more pronounced after salbutamol than after placebo, this could be explained by an additive effect of nebulising an acidic aerosol twice. However, in our first test the fall in $TcPo_2$ related well to the rise of heart rate which persisted for more than one hour after salbutamol. This could indicate that hypoxaemia was due to a systemic effect of salbutamol. Inhaled as well as intravenously administered salbutamol may cause ventilation-perfusion mismatch, which could result from an increase in pulmonary perfusion into relatively less ventilated areas.[5 20] Furthermore, there has been evidence for increased oxygen consumption after salbutamol in monkeys[7] and adult asthmatics,[5] which offers another explanation for the observed hypoxaemia.

As we did not notice any significant effects of salbutamol on lung function, we cannot confirm the findings of other authors that in infants reduction in smooth muscle tone might render the airways less capable of supporting high flow rates during forced expiration.[2 21]

In conclusion we believe that salbutamol does have a pharmacological effect causing hypoxaemia. What we could prove is that acidity itself induces hypoxaemia and may therefore enhance the negative effects of salbutamol. We therefore recommend that nebuliser solutions should be neutralised as far as possible and more information concerning the different properties of the aerosols be made available.

We thank Mrs Heidi Schulenburg and Mrs Angela Meilinger for skilful technical assistance and the nurses from MHH Kinderklinik as well as Kinderkrankenhaus auf der Bult for taking care of the infants.

1 Prendiville A, Rose A, Maxwell DL, Silverman M. Hypoxaemia in wheezy infants after bronchodilator treatment. *Arch Dis Child* 1987;**62**:997–1000.
2 Hughes DM, LeSouef PN, Landau LI. Effect of salbutamol on respiratory mechanics in bronchiolitis. *Pediatr Res* 1987; **22**:83–6.
3 Prendiville A, Green S, Silverman M. Paradoxical response to nebulised salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. *Thorax* 1987;**42**:86–91.
4 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986;**ii**:1424–5.
5 Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax* 1989;**44**:258–67.
6 Beasley CR, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987;**294**:1197–8.
7 Newth C. Pulmonary and metabolic responses to inhaled salbutamol (albuterol) in monkeys (Macaca mulatta). *Am Rev Respir Dis* 1989;**139**:A564.
8 Bouhuys A, van de Woestijne KP. Mechanical consequences of airway smooth muscle relaxation. *J Appl Physiol* 1971; **30**:670–6.
9 Prendiville A, Silverman M. Paradoxical response to nebulised salbutamol in wheezy infants. *Thorax* 1987;**42**: 702–3.
10 Masters IB, Seidenberg J, Hudson I, Phelan PD, Olinsky A. Longitudinal studies of lung mechanics in normal infants. *Pediatr Pulmonol* 1987;**3**:3–7.
11 Seidenberg J, Masters IB, Hudson I, Olinsky A, Phelan PD. Disturbance in respiratory mechanics in infants with bronchiolitis. *Thorax* 1989;**44**:660–7.
12 Radford M. Measurements of airway resistance and thoracic gas volume in infancy. *Arch Dis Child* 1974;**49**:611–5.
13 Zhang YG, Wright WJ, Tam WK, Nguyen-Dang TH, Salome CM, Woolock AJ. Effect of inhaled preservatives on asthmatic subjects. *Am Rev Respir Dis* 1990;**141**:1405–8.
14 Hirshman CA, Peters J, Downes H, *et al*. Citric acid airway constriction in dogs with hyperreactive airways. *J Appl Physiol* 1983;**54**:1101–7.
15 Wilson NM, Chudry N, Silverman M. Role of the oesophagus in asthma induced by the ingestion of ice and acid. *Thorax* 1987;**42**:506–10.
16 Balmes JR, Fine JM, Christian D, Gordon T, Sheppard D. Acidity potentiates bronchoconstriction induced by hypoosmolar aerosols. *Am Rev Respir Dis* 1988;**138**:35–9.
17 Utell MJ, Morrow PE, Speers DM, Darling J, Hyde RW. Airway responses to sulfate and sulfuric acid aerosols in asthmatics. *Am Rev Respir Dis* 1983;**128**:444–50.
18 Fine JM, Gordon T, Thompson JE, Sheppard D. The role of titratable acidity in acid aerosol-induced bronchoconstriction. *Am Rev Respir Dis* 1987;**135**:826–30.
19 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical bronchoconstriction in wheezing infants after nebulised preservative free iso-osmolar ipratropium bromide. *BMJ* 1989;**299**:1433–4.
20 Harris L. Comparison of the effect on blood gases, ventilation, and perfusion of isoproterenol-phenylephrine and salbutamol aerosols in chronic bronchitis with asthma. *J Allergy Clin Immunol* 1971;**49**:63–71.
21 Prendiville A, Green S, Silverman M. Airway responsiveness in wheezy infants: evidence for functional β adrenergic receptors. *Thorax* 1987;**42**:100–4.

Archives of Disease in Childhood 1991; **66**: 676–682

Home monitoring of transcutaneous oxygen tension in the early detection of hypoxaemia in infants and young children

Christian F Poets, Martin P Samuels, Jane P Noyes, Kirsty A Jones, David P Southall

Abstract

Twenty three patients (age range 0·5–40 months) with recurrent cyanotic episodes underwent physiological recordings, including transcutaneous oxygen tension (TcPo$_2$) from a monitor modified for use at home (Kontron 821S). Of 69 episodes in which the arterial oxygen saturation (Sao$_2$, Nellcor N200) was ≤80% for ≥20 seconds and/or central cyanosis was present, the TcPo$_2$ monitor alarmed (≤20 mmHg or 2·67 kPa) in every episode. The pulse oximeter identified hypoxaemia in 62 out of 69 episodes, failing in seven episodes due to signal loss from movement artefact. In only seven of 69 episodes was there an accompanying apnoeic pause (≥20 seconds), and heart rate fell to ≤80 beats/minute in only five of 28 episodes in which an electrocardiogram was recorded. In 32 episodes in which Sao$_2$ fell to ≤60%, the TcPo$_2$ monitor alarmed after a median time interval of 16 seconds (maximum time interval 30 seconds).

The TcPo$_2$ monitor was then used in an uncontrolled trial at home in 350 patients at increased risk of sudden death and/or hypoxaemia. Indications for monitoring included apparent life threatening events or cyanotic episodes (n=163), prematurity and prematurity related disorders (n=86), and sudden unexpected death in one or more siblings (n=122).

The TcPo$_2$ monitor detected cyanotic episodes at home in 81 patients, 52 of whom received vigorous stimulation and/or mouth to mouth resuscitation. Twenty one of these 52 patients had further hypoxaemic episodes documented in hospital with pulse oximetry. In 30 patients, the TcPo$_2$ monitor also identified the gradual development of hypoxaemia, as confirmed by pulse oximetry. Twenty of these needed additional inspired oxygen and six subsequently needed ventilatory support in hospital.

This TcPo$_2$ monitor is a reliable detector of both sudden and gradual onset hypoxaemia and is able to be used by parents in the home.

Department of Paediatrics, National Heart and Lung Institute, Royal Brompton Hospital, Fulham Road, London SW3 6HP
Christian F Poets
Martin P Samuels
Jane P Noyes
Kirsty A Jones
David P Southall

Correspondence to:
Dr Southall.

Accepted 23 January 1991

Electronic monitors are widely used in the home on infants at increased risk of sudden death. Most monitors aim to sense an absence of breathing movements and/or a fall in heart rate. Unfortunately, a considerable number of infants have died while on such monitors.[1–3] One possible explanation, based on our investigations of cyanotic episodes, is that a prolonged absence of breathing movements or a bradycardia is relatively infrequent or late in its timing compared with severe hypoxaemia.[4]

Although the final pathways leading to sudden infant death syndrome (SIDS) remain unknown, the sudden onset of severe hypoxaemia is one cause.[4] Hypoxaemia may occur not only as a result of a cessation in breathing movements, but also as a consequence of upper airway obstruction, seizures, or intrapulmonary shunting.[4 5]

Oxygenation may be monitored continuously and non-invasively by using either pulse oximetry or a transcutaneous oxygen tension (TcPo$_2$) sensor. Pulse oximetry, if used correctly, provides an accurate measure of arterial oxygen saturation (Sao$_2$)[6] and does not require heating of the skin. However, it has the major drawback of signal loss due to motion artefact. TcPo$_2$ monitoring is a well validated technique for the detection of hypoxaemia in preterm infants undergoing neonatal intensive care,[7] but the sensor is more difficult to use, and measurements of oxygenation are substantially affected by skin perfusion (see below).

In this study we investigated a modified TcPo$_2$ monitor in its ability to detect sudden onset hypoxaemia and to be used for the home surveillance of infants at increased risk of sudden death. Three questions were addressed: (i) will the system detect episodes of hypoxaemia reliably and in time for potentially effective intervention; (ii) will the monitor show reproducible baseline readings; and (iii) is the system suitable for long term use by parents in the home in terms of ease of application, frequency of false alarms, and potentially harmful side effects?

Methods

APPARATUS

A standard neonatal TcPo$_2$ monitor was modified (Kontron 821S) to provide (i) a constant, single electrode temperature of 43°C to allow a longer interval between sensor resiting, (ii) an inability to be left in a calibration, non-alarm mode, and (iii) toddler proof alarm controls. The TcPO$_2$ values were displayed in mm Hg so that parents did not have to use decimals. The sensor was calibrated in air (160 mm Hg or 21·30 kPa) before each application. The value of TcPo$_2$ was continuously displayed. The high alarm was set 10 mm Hg (1·33 kPa) higher than the highest level of TcPo$_2$ found on the baby, so that in the event of even slight separation of the sensor from the skin a high alarm (approaching the oxygen tension of air) would sound. The low alarm was usually set to 20 mm Hg (2·67 kPa). The monitor was powered by long life or rechargeable batteries, or through a mains adaptor. It was portable (76×205×104 mm) and provided with a carrying case.

VALIDATION STUDIES

Changes in physiological parameters during sudden onset hypoxaemic episodes

Twenty three infants and young children (median age 5 months, range 2 weeks–40 months) who were having recurrent cyanotic episodes underwent long term multichannel recordings of Sao$_2$ from a pulse oximeter (Nellcor N200, modified to give beat to beat averaging), photoplethysmographic waveforms for the validation of the Sao$_2$ signal, electrocardiography, abdominal wall movements (Graseby volume expansion capsule) and TcPo$_2$ (Kontron 821S). Recordings were performed in the intensive care or high dependency area of the Royal Brompton Hospital and trained cardiothoracic nurses were asked to note all episodes of clinically apparent central cyanosis. Analysis of the recordings included the identification of the number of episodes in which (i) Sao$_2$ fell to 80% or less for at least 20 seconds, and/or (ii) central cyanosis occurred. The association between changes in TcPo$_2$ and other physiological parameters and recorded or observed hypoxaemic episodes was analysed.

Response time

Recordings which showed one or more episodes of severe hypoxaemia (Sao$_2$ $\leq$60% for $\geq$10 seconds) underwent analysis to calculate the time interval for the TcPo$_2$ monitor to alarm (TcPo$_2$ $\leq$20 mm Hg or 2·67 kPa) after the Sao$_2$ reached 60%. A threshold of 60% Sao$_2$ was arbitrarily defined according to clinical experience: cyanosis is usually present at this level if the haemoglobin concentration is within the normal range. In addition, it has been shown that TcPo$_2$ equals arterial oxygen tension minus 14 mm Hg (1·87 kPa) at a sensor temperature of 43°C,[8] and a Sao$_2$ of 60% approximately corresponds with an arterial oxygen tension of 35 mm Hg (4·67 kPa) on the oxygen dissociation curve, which in turn corresponds with a TcPo$_2$ of 20 mm Hg (2·67 kPa).

Baseline measurements, skin status, and false alarms

A sample of 43 parents consecutively entered into the monitoring programme was asked to keep a record of the time and the TcPo$_2$ values before each resiting of the sensor and 20 minutes after the resiting in order to assess the reproducibility of the baseline measurements, the time interval between resitings, and the degree with which readings changed or drifted during each resiting interval. They were also asked to keep a record of the skin status observed after each change of sensor site. This was estimated using a score, which included zero for no mark present, one and two for red marks of different intensities, and three for the presence of a blister. Finally, they were asked to keep a record of alarms in which their baby appeared to be well (false positives) and the reasons for their occurrence, if evident (for example, the sensor lifted from the skin).

CLINICAL TRIAL

Patients

Between May 1988 and November 1990, 350 patients were referred either by their general practitioner (n=47), or community or hospital paediatrician (n=303). Their median age was 2·6 months (range 1 day–5 years). The clinical indications for referral are shown in table 1. Over 95% of patients, according to published information, were considered to be at increased risk of sudden death or hypoxaemia. The majority (93%) had experienced one or more episodes of cyanosis, were born prematurely, or had one or more siblings who died of SIDS. In 14 of the remaining 25 patients the TcPo$_2$ monitor was used to assist parents in the use of negative pressure ventilation at home.[9]

Before the onset of home monitoring, 253 patients (72%) underwent analog tape recordings of Sao$_2$ photoplethysmographic waveforms, breathing movements, electrocardiography, and airflow from either a thermistor (Yellow Spings Instruments) or expired carbon dioxide signals (Engström Eliza). Recordings were not performed in infants who had lost one sibling from SIDS.

Protocol for the use of the monitor at home

Parents and infants were discharged after a minimum of five hours' use of the monitor in hospital, in 82% involving at least one overnight stay. All parents were given detailed verbal and written instruction in the use of the TcPo$_2$ monitor including advice on troubleshooting. For example, in the event of a persistent fall in baseline TcPo$_2$, parents were taught the following sequence of checks to ascertain that this was not artefactual in origin. Firstly, the sensor was

Table 1 Clinical indications for home TcPo$_2$ monitoring in 350 patients

	*No of patients**
ALTE or episodes of cyanosis	**163**
ALTE resolving with cardiopulmonary resuscitation	62
ALTE resolving with vigorous stimulation	72
Cyanotic episodes resolving spontaneously or with mild stimulation	18
Cyanotic breath holding spells	11
Prematurity and prematurity related disorders	**86**
Born $\leq$32 weeks' gestation	76
History of severe apnoea of prematurity	26
Bronchopulmonary dysplasia:	45
Receiving additional inspired oxygen	31
And/or negative pressure ventilation at home	11
SIDS in sibling(s)	**122**
SIDS in one sibling	100
SIDS in two siblings	11
SIDS in twin/triplet	11
Other medical diagnoses	**25**
Sleep related upper airway obstruction	8
Congenital alveolar hypoventilation syndrome	4
Respiratory problems after cardiothoracic surgery	8
Others (myopathy (n=2), parental anxiety, Joubert's syndrome, SVT)	5

*Some patients in more than one category. ALTE=apparent life threatening event, SIDS=sudden infant death syndrome, SVT=supraventricular tachycardia.

recalibrated in air and its site on the skin was changed. If the value remained low, the sensor was placed on the surface of the parents' own forearm. If the reading on the parent was 'normal' (usually >50 mm Hg or 6·67 kPa), the cause of the low baseline value was probably a low blood oxygen tension or a disturbed skin perfusion in the infant. In this event parents were asked to notify their family doctor or local hospital immediately. If the value remained low on the parent's skin the sensor was remembraned and resited first on their forearm and then on their baby.

In those infants with bronchopulmonary dysplasia receiving domiciliary oxygen it was recommended that a reduction in values of $TcPo_2$, which were not artefactual, were followed by an increase in the flow of inspired oxygen to bring the $TcPo_2$ concentration to that which was normal for the baby (depending on recommendations based on pulse oximetry). In this event parents were also asked to contact their local hospital immediately. In hospital the low $TcPo_2$ values were correlated with a pulse oximeter and if hypoxaemia was confirmed the causes for this were treated appropriately.

High alarms due to partial or complete separation of the sensor from the skin were minimised by modifications to the 'sensor to lead junction' and the use of adequate tape over the sensor itself and on the sensor lead. Care was taken not to compress the sensor onto the skin surface or place it over a bony surface since this could reduce skin blood flow and produce low $TcPo_2$ values.

Parents were given instructions on how to manage a severe episode of hypoxaemia needing immediate intervention. This training was provided by a clinical nurse specialist. Instruction included the use of a video, Resusci-doll (Laerdal) and a purpose written handbook on infant resuscitation (available on request). A 24 hour, seven day a week on call service was provided by both clinical nurse specialists and the medical staff involved in the programme. A broken monitor would be replaced within 18 hours.

Parents were thereafter seen at regular visits in the outpatient clinic and either at home or in hospital by the clinical nurse specialist who provided advice and support.

A decision to discontinue monitoring was undertaken in full collaboration with parents and in circumstances appropriate to the medical problems involved. For example, in subsequent siblings of victims of SIDS a post-term age of 9 months was usually chosen (>95% of all cases of SIDS have occurred by this age[10]).

Results

VALIDATION STUDIES

$TcPo_2$ changes during severe hypoxaemic episodes

Of 23 infants with recurrent cyanotic episodes who underwent multichannel recordings (total duration of recordings 340 hours), 16 patients (median age 5 months, range 2 weeks–40 months) had a total of 69 prolonged hypoxaemic and/or cyanotic episodes. Fifty two episodes involved a desaturation on the tape recording; although cyanosis may have been present, it was not specifically documented by the nurses. In 10 episodes, cyanosis was reported by the nurses and confirmed by low Sao_2 readings (fig 1). In a further seven episodes with clinically apparent central cyanosis the Sao_2 signal was uninterpretable due to movement artefact (fig 2). All 69 episodes (100%) were associated with a fall in $TcPo_2$ to $\leqslant 20$ mm Hg (2·67 kPa). Only seven of the 69 episodes were accompanied by a pause in breathing movements of $\geqslant 20$ seconds. In two episodes bag and mask resuscitation was required to initiate recovery

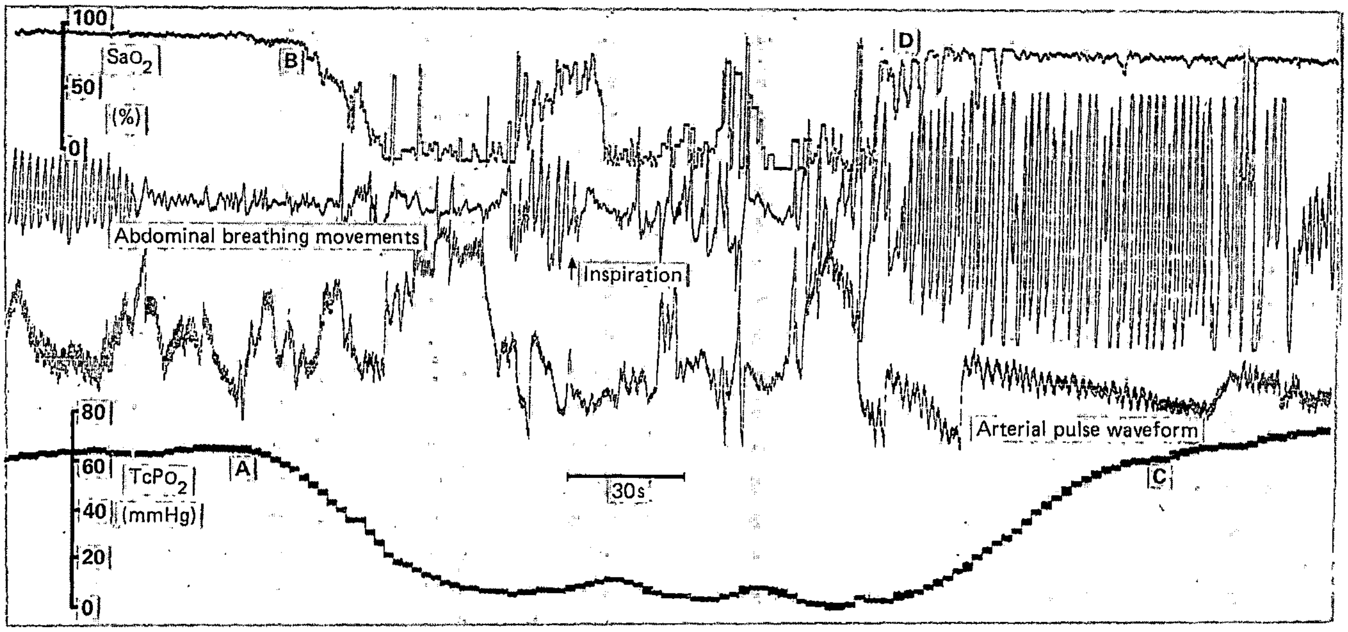


Figure 1 A major hypoxaemic episode in a 2 year old child with recurrent cyanotic episodes. Breathing movements, although reduced in amplitude, continue throughout the hypoxaemic episode (from B to D). Sao_2 (Nellcor N200 in the beat to beat mode) starts to fall at B, and remains low for 150 seconds (to D). The onset of the dip in $TcPo_2$ (from A to C) occurs simultaneously with the onset of the fall in Sao_2. The alarm on the $TcPo_2$ monitor was set at 20 mm Hg (2·67 kPa) and would have sounded 17 seconds after the point at which the Sao_2 reaches 60%. Examination of the arterial pulse (photoplethysmographic) waveforms shows no evidence of a bradycardia. The child, who was deeply cyanosed, was resuscitated with bag and mask ventilation. (1 kPa=7·5 mm Hg.)

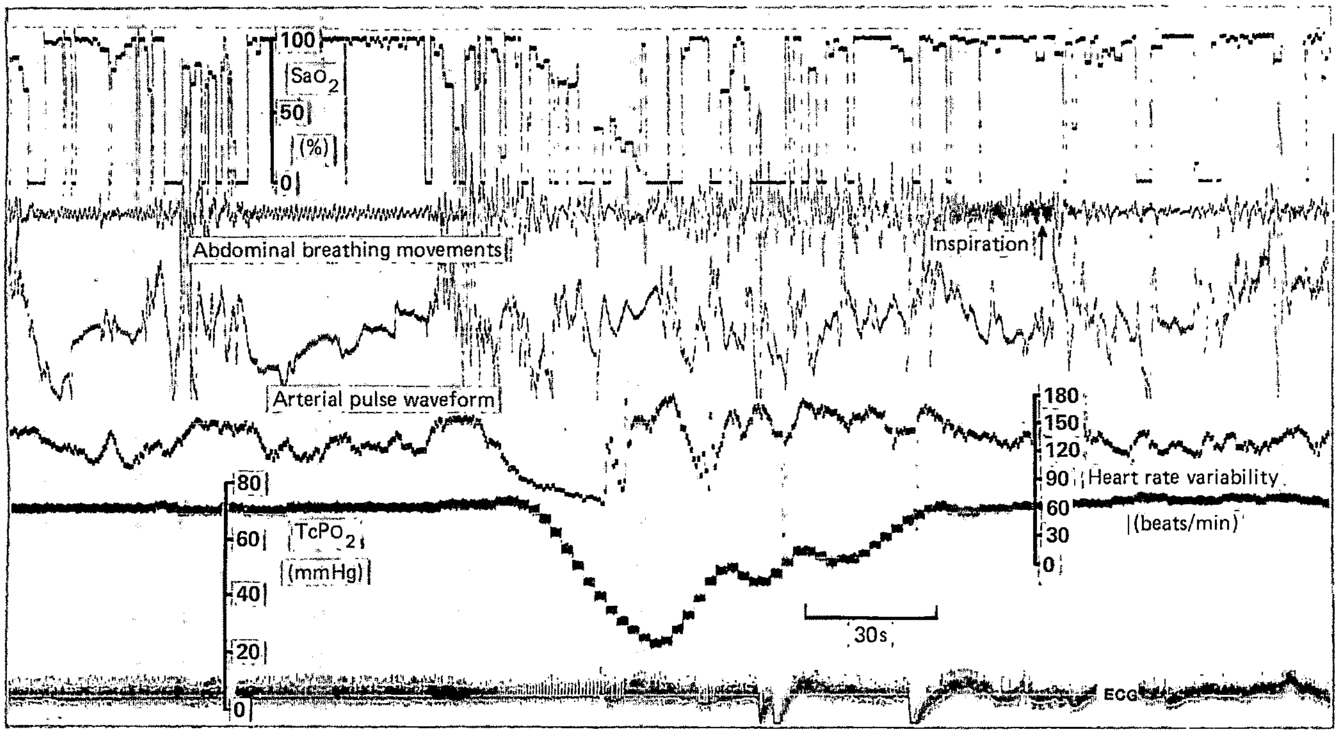


Figure 2 Recording on an infant (aged 2 months) during an episode of cyanosis, at the time of which there is a sudden fall in $TcPO_2$ lasting 90 seconds. This is accompanied by continuous breathing movements and a fall in heart rate to 65 beats/minute. The pulse oximeter signal is lost due to movement artefact and would not therefore have identified this event. (1 kPa=7·5 mm Hg.)

(fig 1), one of these episodes was associated with a prolonged apnoeic pause. In 28 episodes in 10 patients where an electrocardiogram was recorded, bradycardia (heart rate $\leq$80 beats/minute) was present during just five episodes.

Response time

Thirty seven episodes with SaO_2 $\leq$60% for $\geq$10 seconds were identified to have occurred in 16 patients. Five episodes in three patients showed a very slow onset of a fall in SaO_2 (time to reach 60% >1 minute). In all these five episodes $TcPO_2$ reached the 20 mm Hg (2·67 kPa) threshold up to 108 seconds *before* SaO_2 fell to 60%. The median response time in the remaining 32 episodes with a fall in $TcPO_2$ *after* the onset of low SaO_2 readings was 16 seconds, the maximal time observed was 30 seconds. There was no consistent change in the response time with increasing age.

Baseline measurements

Forty one parents (95%) returned the questionnaire. They had been entered into the monitoring programme between five days to four months before receiving the questionnaire. They reported a total of 988 resiting episodes in their infants. The median of the individual mean resiting intervals in these 41 patients was 6·8 hours (interquartile range (IQR) 6·1 to 7·8 hours). The median of the individual mean baseline readings was 59·9 mm Hg (7·98 kPa) (IQR 54·9 to 65·8 mm Hg or 7·32 to 8·77 kPa). There were no differences between different age groups. The median of the individual mean changes in $TcPO_2$ values over an average resiting interval of 6·8 hours was −13 mm Hg (−1·73 kPa) (IQR −8·1 to −17·1 mm Hg or −1·08 to −2·28 kPa).

In order to assess the variability of baseline values on any one infant, SDs were calculated for the individual baseline readings in each infant. The median of these SDs as an indicator for the reproducibility of the baseline readings was 6·9 mm Hg (0·92 kPa) (IQR 5·7 to 7·5 mm Hg or 0·76 to 1·00 kPa). This means that the average variability in two thirds of the baseline readings was within a range of ±7 mm Hg (0·93 kPa).

False positive alarms

A total of 129 false positive alarms (73 high, 56 low) occurred in 30 of the 41 infants during a total monitoring period of 540 days, giving an average for the whole group of one false alarm every four days of monitoring. In the two patients with the highest numbers of false alarms (12 and 16, respectively), the monitor turned out to be faulty. In the remaining infants high alarms were all explained by loose sensor contact and occurred predominantly in the older, more active babies. False low alarms were reported in 20 infants, most of them were associated with a drift downwards in baseline readings or the infant rolling over on to the sensor.

Skin status

A red mark appeared on the skin in 872 (88%) of the 988 sitings. In 838 (96%) of these marks the mark had faded completely after 48 hours. Thirty four marks were reported in 11 infants to have persisted for more than 48 hours, all but two were stage 1 marks (slight redness). In one infant one blister was reported, which occurred after the mother had not changed the sensor site for nine hours.

CLINICAL DATA

Duration of monitoring

Over a 30 month period, 201 infants completed monitoring. In 19 patients (10%) the parents decided to discontinue monitoring before medically advised. The mean (SD) duration of monitoring in patients who completed the programme according to medical advice was 6·9 (3·7) months.

Detection of hypoxaemia

Two patterns of low $TcPo_2$ readings were observed: acute falls in $TcPo_2$ and changes in baseline $TcPo_2$. Acute falls in $TcPo_2$ associated with cyanosis or pallor were observed in 81 patients (table 2). Fifty two of these patients had an apparent life threatening event, needing vigorous stimulation (n=38) or mouth to mouth resuscitation (n=14) for recovery. Thirty nine of these 52 patients had entered the programme because of a previous apparent life threatening event or cyanotic episode, seven were preterm (≤32 weeks' gestational age), and five were siblings of a SIDS victim. Twenty one of the 52 infants had a further hypoxaemic episode, confirmed in hospital by pulse oximetry to be due to arterial desaturation.

Seventy two patients had a persistent fall in the baseline concentrations of $TcPo_2$; in 30 patients these lower values were subsequently confirmed by pulse oximetry in hospital to indicate real hypoxaemia. Most of them were preterm infants (20/30) and 12 had bronchopulmonary dysplasia. Twenty five infants had a respiratory infection. In 20 infants (16 preterm) additional inspired oxygen was given, and in six of these further respiratory support was later necessary. One infant with low baseline readings during a bronchiolitis subsequently suffered an apparent life threatening event needing resuscitation while in hospital.

In the remaining 42 patients with a low baseline $TcPo_2$ identified by parents, this was either proved by pulse oximetry not to represent arterial hypoxaemia (n=13), or the infant was seen by the family doctor and the low readings were not checked against pulse oximetry (n=29). Intercurrent infections, usually respiratory but also gastrointestinal, were subsequently (within one to two days) or simultaneously identified in 35 (83%) of these patients. For example, in one infant (a SIDS sibling) the monitor alarmed at 3 am, reading 13 mm Hg (1·73 kPa). The values remained low, and the family doctor called could not find anything wrong with the infant except for a rectal temperature of 38°C. She was admitted to hospital for observation. Within one hour of admission, three hours after the initial alarm on the monitor, the infant became drowsy and unresponsive. A lumbar puncture revealed *Haemophilus influenzae* meningitis.

Table 2 Outcome of 350 patients undergoing home $TcPo_2$ monitoring

	No of patients
Hypoxaemic episodes with cyanosis or pallor as reported by parents:	**81**
Needed vigorous stimulation or mouth to mouth resuscitation	52
Had further episode in hospital documented by pulse oximetry	21
Baseline decreases in $TcPo_2$ proved to be hypoxaemia (by pulse oximetry):	**30**
Had respiratory infection	25
Needed additional inspired oxygen	20
Needed subsequent respiratory support	6
Discontinued monitor prematurely	**19**
Sudden unexpected deaths	**4**

Deaths during monitoring programme

Four infants have died suddenly despite the parents having been issued with a $TcPo_2$ monitor. The first infant referred at the beginning of the monitoring programme was the twin of a SIDS victim and lived in severely deprived home circumstances. Every effort was made to teach the parents how to use the monitor but on the night of her death it was connected to the infant in the calibration mode, which at that stage of the programme muted the monitor alarms (Kontron 820). The potential danger of this possibility had not been considered by us or the manufacturers but was then overcome by modifying the monitor so that this could not recur (Kontron 821S).

The second infant, who had bronchopulmonary dysplasia and was receiving additional inspired oxygen at home, had demonstrated a major fall in baseline $TcPo_2$ values for two days before his sudden death. His inspired oxygen concentration was progressively raised in an unsuccessful attempt to compensate for this but unfortunately no contact was made with the hospital. On the third day of this increased oxygen requirement he developed sudden and severe cyanosis while crying, progressed to prolonged apnoea,[4] and could not be resuscitated. He was found to be dead on arrival at hospital. A postmortem examination showed bronchopneumonia and bronchopulmonary dysplasia.

A third infant with congenital myopathy died suddenly at home. A postmortem examination showed bronchopneumonia. Unfortunately, without informing us, his parents had substituted a breathing movement detector for $TcPo_2$ monitoring because of an inability to afford the batteries. We now supply rechargeable batteries on loan to financially compromised parents.

The fourth infant, aged 10 months, had suffered recurrent severe cyanotic episodes due to intrapulmonary shunting[4] and requiring resuscitation on multiple occasions at home and in hospital. He died suddenly while asleep but not on the monitor. His mother was convinced despite our advice to the contrary that cyanotic episodes only occurred when he was awake. The certified cause of death was apnoea of infancy.

Additionally, two infants in the monitoring programme died in hospital during severe pneumonia.

Discussion

VALIDATION STUDIES

This $TcPo_2$ monitor showed a sensitivity of

100% in the detection of sudden severe episodes of hypoxaemia or cyanosis. This contrasts with a sensitivity of 90% for pulse oximetry, 10% for breathing movement monitoring, and 18% for electrocardiographic monitoring. $TcPo_2$ measurements respond to changes in arterial oxygen tension and in the delivery of oxygen to the skin (skin perfusion). Perhaps because of associated reflex changes in the latter in response to sudden hypoxaemia,[11] the response time of the $TcPo_2$ signal is relatively short. The median delay when compared with the pulse oximeter in the beat to beat mode was 16 seconds.

As the association between Sao_2 and arterial oxygen tension is influenced by the many factors influencing the oxygen dissociation curve, pulse oximetry cannot serve as a gold standard for the validation of oxygen tension monitoring. In addition, the influence of skin perfusion and its effects on $TcPo_2$ can be considerable. We are careful therefore not to imply that absolute values relating $TcPo_2$ to Sao_2 can be given. This $TcPo_2$ monitor has already been extensively validated against arterial oxygen tension measurements.[12 13] In this study, we set out to investigate the response of the monitor to sudden onset and rapidly developing hypoxaemia. As it is impractical and unethical to obtain repeated arterial blood gas measurements sequentially during the unpredictable and rapid development of the hypoxaemia that occurs during cyanotic episodes, recordings of pulse oximetry, using a well validated instrument in beat to beat averaging mode,[6 14] were considered the most objective measure of clinically relevant changes in oxygenation.

Investigations performed in these patients and in other reported studies have shown that hypoxaemia is a better indicator of dangerous respiratory pathophysiology than is cessation of breathing movements or bradycardia.[4 15] Severe hypoxaemia may also occur despite continued breathing movements and airflow.[16] The use of pulse oximetry could provide a more rapid response time for hypoxaemia. Unfortunately, validated pulse oximetry, although excellent for the non-invasive measurement of oxygenation, is not yet suitable for long term monitoring because of movement artefact (fig 2).

$TcPo_2$ monitors measure skin oxygen, not arterial oxygen tension. Their mode of action results in a sensitive response to changes in peripheral circulation.[11] This response may be of value in identifying potentially dangerous causes of a low cardiac output (for example, cardiac arrhythmia), or of peripheral vasoconstriction (for example, metabolic acidaemia, hypoglycaemia). Hypoxaemia may also cause peripheral vasoconstriction (through sympathetic activity),[11] which may explain why the $TcPo_2$ monitor alarmed before the pulse oximeter readings reached equivalently low values during the relatively slow onset of hypoxaemia. However, further studies are required to investigate these other potentially important functions of the monitor.

The patients in whom our validation studies were performed are not representative of the total population of infants at risk of sudden death in that many were suffering recurrent cyanotic episodes. Regardless of the primary cause of the pathways leading to death, however, it was our contention that $TcPo_2$ would fall early in suddent infant death at home because of arterial hypoxaemia, reduced skin perfusion (reduced cardiac output or peripheral vasoconstriction), or both. Because life threatening episodes are rare, even in epidemiologically defined high risk groups, we considered it was most practical to validate our $TcPo_2$ monitor in infants with recurrent cyanotic episodes.

The variability of the baseline measurements recorded in the questionnaires was considered small enough for parents to become aware of the normal range of oxygen tension values in their baby. There was, however, a downward drift in some patients. This drift usually began after four hours and has been previously reported by others, using the same electrode over a period of six hours.[17]

The high rate of false alarms with conventional home monitoring may lead to severe disturbances in family life.[18] Weese-Mayer *et al* identified false alarms from cardiorespiratory monitors with an average frequency of six per day.[19] In our study, including parents with different levels of technical experience with the monitor and different social backgrounds, false alarms occurred with an average frequency of one every four days of monitoring.

The temporary redness of the skin resulting from the heated sensor is undesirable. However, skin injury is minimised by strictly advising the parents to avoid resiting intervals of more than eight hours with more rapid resiting during fevers or after recent exposure to sunlight. Nevertheless, we are concerned about this skin effect and are investigating alternative ways of overcoming this problem.

CLINICAL DATA

The patients entered into this $TcPo_2$ monitoring programme had heterogeneous problems. However, the majority (93%) came from one of the three well recognised risk groups for sudden infant death (table 1). Nevertheless, it has been questioned whether the subsequent siblings of SIDS victims should be monitored.[20] However, in two recent large population based studies the SIDS incidence in this group was four and six times higher than in the normal population.[21 22] In the latter study, the overall postneonatal mortality rate in the SIDS siblings was 20·8 per 1000.[22]

The $TcPo_2$ monitor identified two kinds of hypoxaemia: sudden onset, short lived episodes and longer term, more gradual changes in baseline oxygenation. Acute, apparently life threatening episodes of hypoxaemia were predominantly found in infants referred because of a previous apparent life threatening event. In 73% of occasions the monitor appeared to identify sudden episodes in time to effectively resuscitate the infant by stimulation alone without the need for mouth to mouth or bag and facemask ventilation (required in the remaining 27%).

Detection of changes in baseline $TcPo_2$ was particularly valuable in preterm patients; particularly in those with bronchopulmonary dysplasia receiving additional inspired oxygen. Our experience is thus similar to that of Lafeber *et al* who found that $TcPo_2$ monitoring was more sensitive than pulse oximetry to changes in oxygenation in infants with bronchopulmonary dysplasia.[23] Such baseline changes often accompanied intercurrent respiratory infections and frequently preceded the clinical symptoms and signs apparent to parents. Because of the propensity of airway hypoxia, hypoxaemia, and acidaemia (from tissue hypoxia) to induce pulmonary hypertension, the early detection of baseline hypoxaemia may avert rapid, life threatening falls in arterial oxygen tension due, for example, to sudden intrapulmonary right to left shunts.[4] The fact that 20 of 30 infants with baseline falls in $TcPo_2$ confirmed to represent arterial hypoxaemia by pulse oximetry in hospital, needed additional inspired oxygen, and six subsequently needed ventilatory support, supports the idea that the early detection of hypoxaemia may prevent progression to life threatening events in the home; particularly in those infants with bronchopulmonary dysplasia.

The detection of baseline falls in $TcPo_2$ shown by pulse oximetry *not* to represent hypoxaemia and presumably therefore indicating changes in skin perfusion still deserves further investigation. As shown in the infant with meningitis, but also during gastrointestinal and respiratory infections, it appears that these low readings are a sensitive and early indicator of infection, probably due to peripheral vasoconstriction associated with the infection. We advise our parents to have their baby checked by their family doctor or local hospital if the low readings on their baby appear to be real (that is, the monitor shows normal readings on the parent).

Our data concerning clinical experiences with the monitor at home are limited in their potential accuracy by the lack of medical or nursing experience of most parents. In 26% of patients the occurrence of further proved hypoxaemic episodes in hospital validated parental observation. To date these can represent the only definitive events detected by the monitor. We are now, however, beginning to combine the $TcPo_2$ monitor with an event recorder. This device senses electrocardiogram, breathing movements, and Sao_2, and stores these data together with the $TcPo_2$ values onto computer disks before and during a low alarm on the $TcPo_2$ monitor. Thus recorded physiological data during apparent life threatening episodes at home will become available.

This is the first time that a monitor which has been used at home has been validated on infants in hospital with observed and documented episodes of severe hypoxaemia. Nevertheless there remains, at present, no proof that this monitor is superior to other monitoring devices in the prevention of SIDS. Moreover, as with all the other existing home monitors, the data on clinical experience of the parents with this monitor at home are uncontrolled and anecdotal. There is absolutely no evidence as yet that this device will effectively reduce the incidence of sudden infant death.

Our thanks go to the families who participated in the monitoring programme: without their enthusiasm and interest its development would have been impossible. We also thank our colleagues for their assistance: A Elia, C Sheridan, and E Picton-Jones; C Harrison, and E Palmer; P Levene, A Holder, W Mindt, and T Rickwood. Finally we thank the organisations who funded the project: Little Ones, Amble and Breath Fund charities; BBC Children in Need Appeal, Marks and Spencer plc, and Salomon Brothers International Ltd; the DHSS.

Our salaries were funded by the Foundation for the Study of Infant Death and National Heart and Chest Hospitals (DPS), Schreier Foundation (MPS), the Deutsche Forschungsgemeinschaft FRG (CFP), the Priory Foundation (KAJ), Kontron UK Ltd (JPN), and Cot Death Research.

1 Davidson Ward SL, Keens TG, Chan LS, *et al.* Sudden infant death syndrome in infants evaluated by apnea programs in California. *Pediatrics* 1986;**77**:451–8.

2 Rahilly PM. Pneumographic studies: predictors of future apnoeas but not sudden infant death in asymptomatic infants. *Aust Paediatr J* 1989;**25**:211–4.

3 Light MJ, Sheridan MS. Home monitoring in Hawaii: the first 1,000 patients. *Hawaii Med J* 1989;**48**:304–27.

4 Southall DP, Samuels MP, Talbert DG. Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death. *Arch Dis Child* 1990;**65**:953–61.

5 Southall DP. Role of apnea in the sudden infant death syndrome: a personal view. *Pediatrics* 1988;**81**:73–84.

6 Southall DP, Bignall S, Stebbens VA, *et al.* Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987; **62**:882–8.

7 Lucey JF. Clinical uses of transcutaneous oxygen monitoring. *Adv Pediatr* 1981;**28**:27–56.

8 Löfgren O, Jacobson L. The influence of different electrode temperatures on the recorded transcutaneous pO_2 level. *Pediatrics* 1979;**64**:892–7.

9 Samuels MP, Southall DP. Negative extrathoracic pressure in treatment of respiratory failure in infants and young children. *BMJ* 1989;**299**:1253–7.

10 Grether JK, Schulman J. Sudden infant death syndrome and birth weight. *J Pediatr* 1989;**114**:561–7.

11 Suichies HE, Aarnoudse JG, Okken A, Jentink HW, de Mul FFM, Greve J. Skin blood flow changes during apneic spells in preterm infants. *Early Hum Dev* 1989;**20**:155–63.

12 Eberhard P, Mindt W. Reliability of cutaneous oxygen measurement by skin sensors with large-size cathodes. *Acta Anaesthesiol Scand* 1978;**68**(suppl):20–7.

13 Pollitzer MJ, Whitehead MD, Reynolds EOR, Delpy D. Effect of electrode temperature and in vivo calibration on accuracy of transcutaneous estimation of arterial oxygen tension in infants. *Pediatrics* 1980;**65**:515–22.

14 Fanconi S, Doherty P, Edmonds JF, *et al.* Pulse oximetry in pediatric intensive care: comparison with measured saturations and transcutaneous oxygen tension. *J Pediatr* 1985; **107**:362–6.

15 Long JG, Philip AGS, Lucey JF. Excessive handling as a cause of hypoxemia. *Pediatrics* 1980;**65**:203–7.

16 Poets CF, Stebbens VA, Samuels MP, Southall DP. Patterns of breathing during hypoxaemia in preterm infants at around term (abstract). *Early Hum Dev* 1990;**22**:107–8.

17 le Souef PN, Morgan AK, Soutter LP, *et al.* Continuous comparison of transcutaneous and arterial oxygen tension in newborn infants with respiratory illnesses. *Acta Anaesthesiol Scand* 1978;**68**(suppl):91–7.

18 Desmarez C, Blum D, Montauk L, Kahn A. Impact of home monitoring for sudden infant death syndrome on family life. *Eur J Pediatr* 1987;**146**:159–61.

19 Weese-Mayer DE, Brouillette RT, Morrow AS, *et al.* Assessing validity of infant monitor alarms with event recording. *J Pediatr* 1989;**115**:702–8.

20 Little GA, Ballard RA, Brooks JG, *et al.* National Institutes of Health consensus development conference on infantile apnea and home monitoring, Sept 29 to Oct 1, 1986. *Pediatrics* 1987;**79**:292–9.

21 Irgens LM, Skjaerven R, Peterson DR. Prospective assessment of recurrence risk in sudden infant death syndrome siblings. *J Pediatr* 1984;**104**:349–51.

22 Guntheroth WG, Lohmann R, Spiers PS. Risk of sudden infant death syndrome in subsequent siblings. *J Pediatr* 1990;**116**:520–4.

23 Lafeber HN, Fetter WPF, van der Wiel AR, Jansen TC. Pulse oximetry and transcutaneous oxygen tension in hypoxemic neonates and infants with bronchopulmonary dysplasia. *Adv Exp Med Biol* 1987;**220**:181–6.

Children with uncontrolled seizures can gain control of their lives

Sabril can have a dramatic effect on the lives of children with epilepsy.

Almost 50% of children with uncontrolled epilepsy who have had Sabril added to their existing therapy have shown a good to excellent response. Some have become seizure free.(1)

Sabril is generally well tolerated and can be administered conveniently in either single or divided daily doses.

▼ SABRIL®

VIGABATRIN

Specific GABA-transaminase inhibition
for uncontrolled epilepsy

MERRELL
DOW

Merrell Dow Pharmaceuticals Limited, Lakeside House, Stockley Park, Uxbridge, Middlesex UB11 1BE
Trademarks: Merrell, Dow, Sabril.

Abridged Prescribing Information

SABRIL▼ Tablets

Presentation: White tablets with a breakline marked SABRIL, each containing 500mg vigabatrin.
Uses:
Indications: Treatment of epilepsy not controlled by other antiepileptic drugs.
Dosage and Administration: Oral administration once or twice daily added to the patient's current therapeutic regimen.
Adults: Recommended starting dose 2g/day. Increased or decreased in 0.5g or 1.0g increments depending upon clinical response and tolerability. Maximum 4g/day.There is no direct correlation between plasma concentration and efficacy.
Children: Recommended starting dose 1g/day in ages 3-9 years and 2g/day if older.
Elderly: Consider dose reduction in patients with impaired renal function.
Contra-indications, Precautions, Warnings etc
Use in pregnancy and lactation: Contra-indicated.
Precautions: Abrupt withdrawal may lead to rebound seizures.Caution in patients with history of psychosis or behavioural problems.Caution in elderly patients, particularly creatinine clearance below 60ml/min. Reduce dose and monitor closely for adverse events.
Warnings: Vigabatrin causes intramyelinic oedema in the brain white matter tracts of animals but there is no evidence of this in man. However, monitor patients for neurological changes. See the full product data sheet.
Effects on driving ability: Drowsiness has been seen and patients should be warned.
Side effects: Are mainly CNS related. Aggression and psychosis have been reported and a previous history of psychosis or a behavioural problem appears to be a predisposing factor. Other reported events: drowsiness and fatigue, dizziness, nervousness, irritability, depression, headache and less commonly confusion, memory disturbance and vision complaints; also weight gain and minor gastrointestinal side-effects. Also in children excitation and agitation.Some patients may experience an increase in seizure frequency with vigabatrin, particularly those with myoclonic seizures.Tests have not revealed evidence of neurotoxicity in humans.Lab data do not indicate renal or hepatic toxicity. Decreases in SGOT and SGPT have been observed. Chronic treatment may lead to a slight decrease in haemoglobin.
Drug Interactions: Are unlikely. A gradual reduction of about 20% in plasma phenytoin concentration has been observed. No clinically significant interactions with carbamazepine, phenobarbitone or sodium valproate.
Legal Category: POM
Package Quantities: Blister strips of 10 in cartons of 100.
Product Licence Number: PL 4425/0098
NHS Price: £46.00
Date of Preparation: November 1990.
You must refer to the full prescribing information before administering Sabril. Further information including full product data sheet is available from the Licence Holder: Merrell Dow Pharmaceuticals Ltd, Lakeside House, Stockley Park, Uxbridge, Middlesex, UB11 1BE

Reference:
1. Livingston J *et al* (1989) Br J Clin Pharm 27 (Suppl 1): 1095–1125

JOB NO: SAB 0691

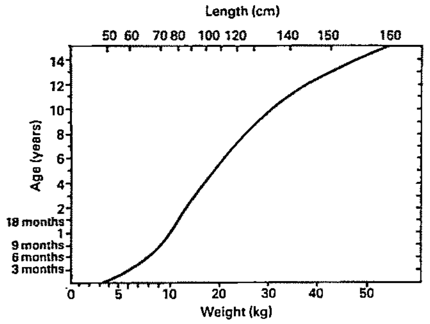
TRADEMARKS: Sabril, Merrell, Dow.

MERRELL
DOW

Endotracheal tube

Length (cm)	Internal diameter (mm)
18–21	7·5–8·0
18	7·0
17	6·5
16	6·0
15	5·5
14	5·0
13	4·5
12	4·0 3·5
10	3·0–3·5

Paediatric resuscitation chart



Adrenaline (ml of 1/10 000) intravenous or endotracheal	0·5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal	0·1	0·2	0·4	0·6	0·6	0·6
Bicarbonate (ml of 8·4%) intravenous	5	10	20	30	40	50
Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
Diazepam (mg) intravenous per rectum	1·25 2·5	2·5 5	5 10	7·5 —	10 —	10 —
Glucose (ml of 50%) intravenous	10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal	5	10	20	30	40	50
Salbutamol (μg) intravenous	25	50	100	150	200	250
Initial DC defibrillation (J)	10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)	50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml ≡ 1·5 ml calcium chloride 10% ≡ 4·5 ml calcium gluconate 10%

A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

Poster: UK £3.50; Abroad £4.50 including packing and postage, by air abroad.
Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.
Credit cards are accepted: ACCESS, VISA, AMERICAN EXPRESS (please give full details)

BMJ BRITISH MEDICAL JOURNAL, BMA HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR

Archives of Disease in Childhood 1991; **66:** 683–685

Changes in periurethral microflora after antimicrobial drugs

K-J Lidefelt, I Bollgren, C E Nord

Deparment of Paediatrics, Karolinska Institute, Sachs' Children's Hospital, PO Box 17912, S-118 95 Stockholm, Sweden
K-J Lidefelt
I Bollgren

Department of Bacteriology, National Bacteriological Laboratory, Stockholm, Sweden
C E Nord

Correspondence to:
Dr Lidefelt.

Accepted 27 December 1990

Abstract

The periurethral flora was examined in 18 girls by use of a quantitative sampling method before, during, and three weeks after treatment with antibiotics for upper respiratory tract infections. Eight girls received amoxicillin. In five of them the anaerobic flora showed a reduction in total counts and in numbers of different species, and all eight girls got a heavy colonisation with enterobacteria during treatment. Three weeks after treatment the anaerobic and aerobic flora had reversed to the pretreatment composition. In 10 girls treated with trimethoprim-sulphamethoxazole the anaerobic flora remained unaffected and no enterobacterial overgrowth was registered during the study period. We propose that antibiotics could be one among several factors involved in the pathogenesis of urinary tract infection, by suppression of the anaerobic microflora and promotion of the colonisation with enterobacteria.

The periurethral microflora in healthy females is dominated by anaerobic bacteria with only scanty growth of aerobic Gram negative rods.[1 2] In females prone to recurrent urinary tract infections, the periurethral region is often colonised with uropathogens, even during infection free intervals.[2–4] A disturbed anaerobic microflora is also found.[5] The normal flora on various body surfaces provides a natural defence against colonisations with new potentially pathogenic bacteria, that is, 'colonisation resistance'.[6–8] Antibiotics may disturb the colonisation resistance and thereby facilitate the development of infections.

The present study is part of a project investigating factors involved in the pathogenesis of urinary tract infection, and examines the effects of antibiotics on the periurethral microflora in girls treated for upper respiratory tract infections and with no history of urinary tract infection. The aims were to investigate the effects on the predominant anaerobic flora and the concomitant effects on colonisation with Gram negative aerobic bacteria.

Subjects and methods

SUBJECTS

Eighteen prepubertal girls (aged 3–13 years, median 4 years) were included in the study. They all attended the emergency ward for otitis media and upper respiratory tract infections, requiring antibiotic treatment. None had a history of urinary tract infection or had been treated with antibiotics during the three month period before entering the study. Informed parental consent were given in all cases.

STUDY DESIGN

Ten girls were treated with trimethoprim-sulphamethoxazole (6 mg trimethoprim and 40 mg sulphamethoxazole/kg/day) and eight girls with amoxicillin (50 mg/kg/day) orally for five to seven days. Sampling of periurethral bacteria was performed immediately before treatment, on the last day of medication, and three weeks after termination of the antibiotic course.

METHODS

The aerobic and anaerobic periurethral flora were examined by a quantitative sampling method.[1] A 5 ml plastic syringe filled with sterile 12% gelatin (Difco), was cut at the needle end of the syringe and the gelatin part was pressed against the urethral orfice. A 2 mm slice of gelatin with the bacteria bearing surface (about 1 cm^2) was cut off and dissolved in 1·8 ml prereduced anaerobic buffer solution. All samples were transported to the laboratory in an anaerobic jar (GasPac System, Becton and Dickinson), and further handled within 60 minutes after collection.

To cultivate the aerobic and anaerobic flora the gelatin was dissolved and serial dilutions (1/10, 1/100, 1/1000) were made. Portions (0·1 ml) of the gelatin sample and from each dilution step were spread onto blood agar plates and incubated in an anaerobic jar at 37°C for five

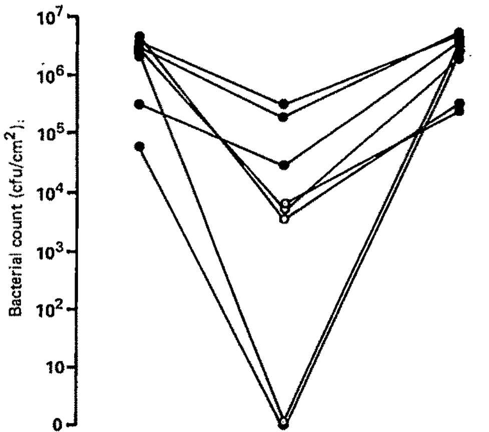


Figure 1 The periurethral anaerobic microflora in eight girls before, during, and three weeks after treatment with amoxicillin (○=growth of ≤2 species).

days. A parallel cultivation for estimation of aerobic bacteria was performed on cysteine-lactose-electrolyte deficient and hematin agar plates incubated aerobically at 37°C for 18 hours.

To quantitate and identify the micro-organisms total counts and counts of different organisms based on colony morphology were registered. The three predominant colony types growing on the anaerobic media were selected and one colony from each of them was isolated and incubated anaerobically and aerobically to test air tolerance. Further identification of each anaerobic isolate was performed by Gram staining, gas-liquid chromatography, and biochemical tests.[9] Total aerobic bacterial counts were estimated and all isolates were Gram stained and identified by standard laboratory procedures.[10]

The study was approved by the ethics committee, Södersjukhuset, Stockholm.

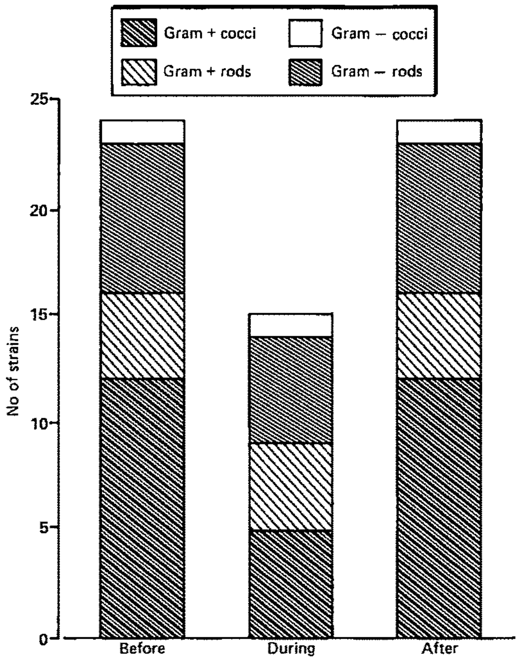


Figure 2 Gram staining properties of anaerobic bacteria in periurethral samples obtained before, during, and three weeks after treatment with amoxicillin.

Results

TREATMENT WITH AMOXICILLIN

Total counts of periurethral anaerobic bacteria/cm^2 in samples obtained before, during, and three weeks after treatment with amoxicillin is shown in fig 1. Before treatment all eight girls showed total bacterial counts ranging between 10^4-10^7 colony forming units (cfu)/cm^2. Five to seven different types of micro-organisms were registered in each sample. During antibiotic treatment total bacterial counts were reduced >3 log cycles in five of eight girls. In these five girls, a reduced number of colony types was also found. In three samples only two different species were recovered, and in the remaining two no anaerobes could be isolated. However, the proportions of different types of micro-organisms remained unaffected when grouped according to Gram staining properties (fig 2). Three weeks after treatment, total counts and numbers of different micro-organisms were similar to that before start of treatment (fig 1). Colonisation with enterobacteria during amoxicillin treatment is shown in fig 3. Before treatment two of eight girls harboured moderate numbers of enterobacteria. During treatment a dense growth with enterobacteria was registered in all eight girls (six *Escherichia coli* strains and two klebsiella strains). Three weeks after termination of treatment no enterobacteria could be recovered from any of the eight girls.

TREATMENT WITH TRIMETHOPRIM-SULPHAMETHOXAZOLE

In the group treated with trimethoprim-sulphamethoxazole total counts of anaerobic bacteria before treatment ranged between 10^4–10^7 cfu/cm^2 (fig 4). During and after treatment no major changes were registered in total bacterial counts or numbers of different micro-organisms. All 10 girls were free from aerobic enterobacterial colonisation throughout the study period (fig 3).

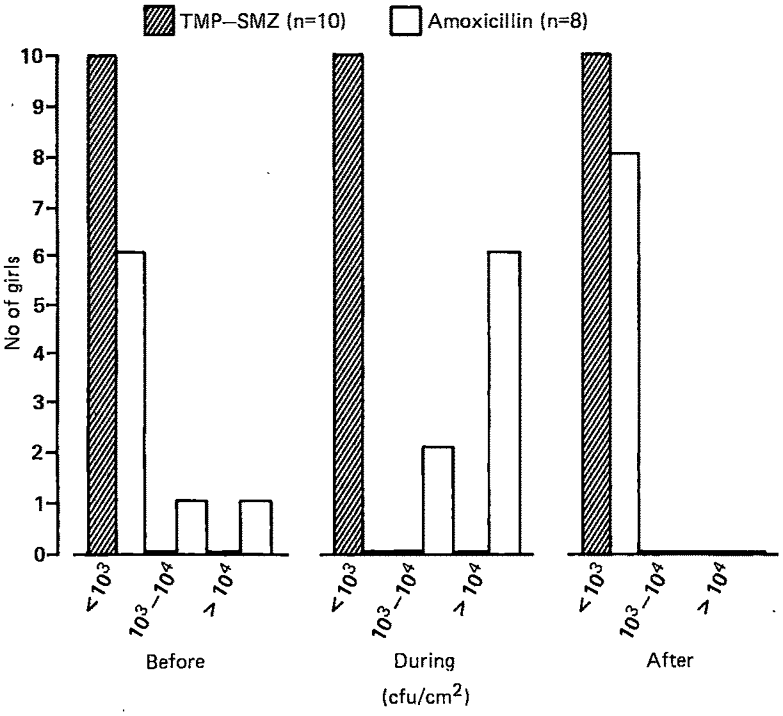


Figure 3 The aerobic, Gram negative periurethral flora before, during, and three weeks after treatment with amoxicillin and trimethoprim-sulphamethoxazole (TMP-SMZ).

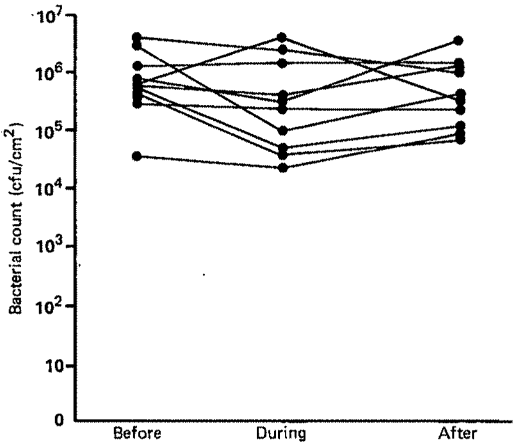


Figure 4 The periurethral anaerobic microflora in 10 girls before, during, and three weeks after treatment with trimethoprim-sulphamethoxazole.

Discussion

The present study showed that treatment with amoxicillin reduced the normal periurethral anaerobic flora and promoted colonisation with Gram negative enterobacteria, whereas trimethoprim-sulphamethoxazole did not influence the normal periurethral flora. Colonisation of the periurethral region is a first step in ascending urinary tract infection.[2 3] The basic defect responsible for this lowered colonisation resistance against uropathogens is still unknown. Among host factors an abnormal anaerobic microflora may be involved, and consequently, antibiotics might interact in the development of urinary tract infection by suppression of the normal microflora. Clinical support for this hypothesis is the finding that children with pyelonephritis had been treated with antibiotics for respiratory tract infections before onset of urinary tract infection significantly more often than a control group.[11]

There are only few previous studies reporting on the effect of antibiotics on the periurethral flora. In monkeys local flushing with amoxicillin facilitated colonisation with uropathogenic *E coli* originating from the intestinal flora.[12 13] Two different studies on women treated with amoxicillin for urinary tract infection showed periurethral colonisation with resistant enterobacteria and suppression of the indigenous lactobacillus population, respectively.[14 15]

The present study shows a heavy colonisation with enterobacteria coinciding with a suppressed anaerobic periurethral flora during amoxicillin treatment, agreeing well with these previous studies. Our findings are also consistent with studies of other microbiotas where eradication of the normal floras by antibiotics was rapidly followed by overgrowth with potential pathogens.[16–19] We have recently shown that anaerobic periurethral bacteria in healthy girls were highly susceptible in vitro to several commonly used antibiotics, including ampicillin, whereas a majority of strains were relatively resistant to trimethoprim-sulphamethoxazole.[20] Our in vivo data, with reduction of the anaerobic flora during amoxicillin treatment and an unaffected microflora during trimethoprim-sulphamethoxazole treatment, accord well with these previous in vitro data. Apparently, the impact on the anaerobic flora varies with different antibiotics.

This study thus supports the concept that a disturbed periurethral anaerobic microflora is associated with a pathological colonisation with enterobacteria, which may be a factor of importance in pathogenesis of urinary tract infection. However, it is still a matter of question what part preceding treatment with antibiotics plays for the emergence of urinary tract infection, as the disturbances of the periurethral flora caused by antibiotics in this study differ from findings in individuals prone to urinary tract infection in certain important respects. The periurethral flora rapidly became normal in these healthy girls after withdrawal of antibiotic treatment, indicating a basic inherent stability of the periurethral ecosystem. In individuals prone to urinary tract infection on the other hand a more persistent pathological colonisation is present, eventually leading to an ascending infection. In our healthy individuals there was a reduction in total counts of anaerobic bacteria, but the proportion of different types of micro-organisms did not change during antibiotic treatment. This contrasts with previous studies on girls prone to urinary tract infection, which showed a disturbed composition of the anaerobic flora.[4] The basic defect explaining the persistent enterobacterial periurethral colonisation in females prone to urinary tract infection thus remains unknown.

Hypothetically, in a population with a lowered resistance against urinary tract infection, the adverse effect of antibiotics on the periurethral flora could be a triggering factor in the development of ascending urinary tract infection.

We wish to thank Ms Ann Lindmark for skilful laboratory assistance and the staff of the emergency ward for valuable help. This study was supported by the Swedish Medical Research Council, Grant No 19X765, the Swedish Society of Medicine and the Samariten Foundation.

1 Bollgren I, Källenius G, Nord CE, Winberg J. Periurethral anaerobic microflora of healthy girls. *J Clin Microbiol* 1979; **10**:419–24.

2 Stamey TA, Timothy M, Millar M, Mihara G. Recurrent urinary tract infections in adult women. The role of introital bacteria. *California Medicine* 1971;**115**:1–19.

3 Bollgren I, Winberg J. The periurethral aerobic bacterial flora in girls highly susceptible to urinary infections. *Acta Paediatr Scand* 1976;**65**:81–7.

4 Brumfitt W, Gargan RA, Hamilton-Miller JM. Periurethral enterobacterial carriage preceding urinary infection. *Lancet* 1987;**ii**:74–80.

5 Bollgren I, Nord CE, Pettersson L, Winberg J. Periurethral anaerobic microflora in girls highly susceptible to urinary tract infections. *J Urol* 1981;**125**:715–20.

6 van der Waaij D, Berghuis-de Vries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *Journal of Hygiene* 1971;**69**:405–11.

7 van der Waaij D, de Vries-Hospers HG, Welling GW. The influence of antibiotics on gut colonization. *J Antimicrob Chemother* 1986;**18**(suppl C):155–8.

8 Mackowiak PA. The normal microbial flora. *N Engl J Med* 1982;**307**:83–93.

9 Holdeman LV, Cato EP, Moore EC. *Anaerobic laboratory manual*. Blacksburg, Virginia: Virginia Polytechnic Institute and State University, 1977.

10 American Association for Microbiology. *Manual of clinical microbiology*. Washington: American Association for Microbiology, 1985.

11 Mårild S, Jodal U, Mangelius L. Medical history among children with acute pyelonephritis compared to controls. *Pediatr Infect Dis J* 1989;**8**:511–5.

12 Herthelius M, Hedström K-G, Möllby R, Nord CE, Pettersson L, Winberg J. Pathogenesis of urinary tract infections—amoxicillin induces genital Escherichia coli colonization. *Infection* 1988;**16**:263–6.

13 Herthelius M, Möllby R, Nord CE, Winberg J. Amoxicillin promotes vaginal colonization with adhering Escherichia coli present in feces. *Pediatric Nephrology* 1989;**3**:443–7.

14 Ronald R, Jagdis FA, Harding GKM, Hobas SA, Muir PL, Gurwith MJ. Amoxicillin therapy of acute urinary tract infections in adults. *Antimicrob Agents Chemother* 1977;**11**: 780–4.

15 Reid G, Bruce AW, Cook R, Llano M. Effect on urogenital flora of antibiotic therapy for urinary tract infection. *Scand J Infect Dis* 1990;**22**:43–7.

16 Sprunt K, Redman W. Evidence suggesting importance of role of interbacterial inhibition in maintaining balance of normal flora. *Ann Intern Med* 1968;**68**:579–90.

17 Bennet R, Eriksson M, Nord CE, Zetterström R. Suppression of aerobic faecal flora in newborns receiving parenteral gentamicin and ampicillin. *Acta Paediatr Scand* 1982;**71**: 559–62.

18 Freter R. The fatal enteric cholera infection in the guinea pig achieved by inhibition of normal enteric flora. *J Infect Dis* 1955;**97**:57–65.

19 Heimdahl A, Nord CE. Effect of erythromycin and clindamycin on the indigenous human anaerobic flora and new colonization of the gastrointestinal tract. *Eur J Clin Microbiol* 1982;**1**:38–48.

20 Lidefelt K-J, Bollgren I, Nord CE, Wiman A. Antibiotic susceptibility of periurethral anaerobic microflora in health girls. *Drugs Exp Clin Res* 1991 (in press).

Archives of Disease in Childhood 1991; **66**: 686–688

Evaluation of a pen injector system for growth hormone treatment

Peter D Gluckman, Wayne S Cutfield

Abstract

The increasing use of human growth hormone (hGH) treatment has resulted in the introduction of a number of alternative delivery systems to conventional syringe and needle administration. We examined patients' evaluation of a new delivery system, the Kabipen (KabiVitrum). We also assessed the accuracy of hGH delivery by the Kabipen. Of the 77 survey respondents 13 had used only the Kabipen, 14 the syringe only, and 50 had used both systems. Altogether 46 (92%) of those who had used both systems preferred the Kabipen. Children over 10 years were more likely to self administer hGH with the Kabipen (64%) than syringe (25%). Patient instructions, convenience of use, and comfort of use were rated better for the Kabipen than syringe. With a dose setting of 2 units the Kabipen delivered a mean (SD) of 1·997 (0·073) units with 102·5% recovery from a unit cartridge. In summary the Kabipen is an accurate device clearly preferred by the majority of hGH recipients surveyed.

Clinicians prescribing human growth hormone (hGH) are aware of the problems that limit the acceptance of this form of treatment by many families. Recent studies have unequivocally shown the value of daily rather than traditional injections three times a week.[1 2] With the rapid increase in utilisation of hGH as a result of its wider availability alternative delivery systems have been developed to facilitate ease of administration.

The traditional form of hGH formulation has been a single dose vial, which had to be reconstituted with diluent for each injection. More recently multiple dose vials have been developed in which several doses can be drawn into syringes from a single reconstituted vial. Most recently a device originally developed for insulin administration, the pocket injector pen,[3] has been applied to hGH treatment. Although some hGH injector pens still require reconstitution of the powdered formulation in vials and transfer to the injector unit, others utilise specific vials for the injector device and thus minimise patient involvement and error in preparing the formulation. New Zealand was the first country to licence a pen for hGH treatment and the purpose of this paper is to review our experience. We report on the results of a blinded questionnaire of patients and their families which compared the injector pen with conventional syringe administration. We also report on the accuracy and economy of the injector pen relative to earlier formulations.

Department of Paediatrics, University of Auckland, Private Bag, Auckland, New Zealand
Peter D Gluckman
Wayne S Cutfield

Correspondence to:
Dr Cutfield.

Accepted 5 February 1991

Methods

At the time of this survey, all patients received one of three formulations (Genotropin, KabiVitrum, Stockholm) of recombinant hGH: 4 unit single dose vials, 12 unit multiple dose vials, or the Kabipen (KabiVitrum) system. The latter consists of an injector pen into which is inserted a 16 unit cartridge of recombinant hGH. The powdered hormone and diluent within the cartridge are in separate compartments. Automatic mixing occurs with insertion of the cartridge into the pen which is then available for multiple and variable (0·5–4 units) dose selection over several days without further preparation. The pen was licenced in New Zealand in June 1989.

The survey evaluating modes of hGH treatment was conducted in April 1990. Of the 105 children on the hGH treatment register, questionnaires were sent to 96 with current addresses.

Anonymous questionnaires were completed by the parent in conjunction with the subject receiving hGH. The questionnaire complied with the guidelines of the human subjects research ethical committee of the University of Auckland.

The questionnaire evaluated the respondent's perception of: the benefits of the injector pen compared with conventional syringe based hGH treatment, the adequacy of patient/family instruction on use of hGH administration, satisfaction regarding information provided on the growth disorder, and on the response to treatment.

Subject preference with explanation was requested of those who had used both systems. Subjects were asked to rate the quality of instructions provided, the convenience of use, and the comfort of use for each type of delivery system they had used. The subject was also asked to comment on whether the system could be improved and to detail technical or practical problems with the device. Qualitative scales were also used to rate satisfaction with the clinical service provided.

Both of the authors randomly and independently evaluated the accuracy of the hormone delivery systems. A random selection of pens was used to deliver eight doses of 2 units each into preweighed vials. The needle was replaced after each dose. The manufacturer's instructions for priming and delivery were followed exactly. By weighing the vial before and after priming and at the end of the delivery of the eighth dose the actual delivery from a 16 unit vial was assessed. Similarly the accuracy and recovery from 12 unit vials was carefully assessed by the authors using 1 ml B-D plastipak syringes (Becton-Dickinson) with microfine III needles. The syringe and needle were replaced after every second dose.

DATA ANALYSIS

Statistical analysis was by non-parametric techniques as the ratings used a ordinal not interval scale. The Mann-Whitney test was used for two sample comparison, the Kruskal-Wallis test for oneway analysis of variance, and the Wilcoxon matched pair signed rank test for paired data; χ^2 analysis was used for frequency distribution analysis.

Results

Of 80 returned questionnaires three were excluded from the analysis: one had discontinued treatment, one had yet to start, and one return was incomplete. The analysis is based on a 83% response rate.

Fifty respondents had used both the syringe and injector pen system. Fourteen had used only a syringe system and of these nine were currently using a multiple dose vial and five were using the 4 unit vial. Thirteen had used only the injector pen—the latter were those most recently placed on hGH treatment.

The hormone was self administered in 35 subjects and by a parent for the remaining subjects except for one infant where the hormone was administered by a visiting nurse. When the analysis was restricted to children 10 years or older, self administration was far more likely using the injector pen (64%) than the syringe (25%, $p<0{\cdot}04$) (table 1).

The most useful sources of patient education with regard to hGH administration were clearly the clinic nurse and/or videotaped administration demonstration (67% of respondents). Other health professionals (9%), pharmaceutical representatives (8%), doctors (7%), and written material (4%) played only a minor role.

There were appreciable differences when patient evaluation of the injector pen and syringe delivery systems were compared (table 2). Of the 50 respondents who had used both delivery systems, 92% indicated a preference for the injector pen. The quality of instructions ($p<0{\cdot}01$), the convenience of use ($p<0{\cdot}01$), and the comfort of use ($p<0{\cdot}01$) were rated significantly better for the injector pen than for the syringe systems (table 2). When the small number of respondents who had used only the pen (n=13) or syringe (n=14) were compared, there were no differences in patient evaluation.

Table 1 Administration of hGH

	Total study (n=77)		*Subjects ≥10 years (n=55)**	
	Pen users	*Syringe users*	*Pen users*	*Syringe users*
Subject	31	4	30	2
Care giver	32	10	17	6

*$p<0{\cdot}05$ by χ^2 test.

Table 2 Comparison of both systems by respondents who used both (mean score, n=50)*

	Pen	*Syringe*	*p Value†*
Quality of instructions	1·5	2·3	<0·01
Convenience of use	1·3	3·3	<0·01
Comfort of use	2·2	3·5	<0·01

*A 1–5 rating system was used with 1 indicating the most favourable response.
†Mann-Whitney test.

Table 3 Accuracy of 2 unit delivery

	Kabipen (n=35)†	*Genotropin* 12 unit vial (n=18)†*
Mean (SD) (units)	1·997 (0·073)	2·000 (0·067)
Coefficient of variation (%)	3·35	3·33
Experimental range (units)	1·87–2·08	1·82–2·06

*Delivered by B–D plastipak 1 ml syringe and microfine III needle.
†Number of doses weighed.

Of the 63 injector pen users, 13 had minor problems in the initial month of use solved by further training. Eleven pens were replaced because of mechanical problems; however of these nine were from the first production batch and occurred in the first months after licensing. Subsequently mechanical problems have not been encountered. Only two subjects had switched back to a syringe system, both because they found the pen heavy to use and had been on a syringe system for some years previously.

The injector pen and syringe systems are of comparable accuracy with the coefficient of variation for the delivery of a 2 unit dose being 3·5% and 3·3% respectively (table 3). The recovered hormone from a vial averaged 102·5% in the pen system and 100% for the 12 unit vial system.

Discussion

Relatively little consideration has been given to the patient perspective for hGH treatment. Historically this reflects the fact that until recently restrictions on hGH supply and the generally non-commercial origin of the hormone meant that there was little motivation to consider these apsects. However the use of hGH has increased considerably after the introduction in 1985 of commercially produced recombinant hGH.[4–8] The range of indications continues to broaden and it is now generally accepted that daily injections are the minimum frequency for an optimal growth response.[9] It is now evident that hGH should be prescribed in relation to body size rather than as the traditional fixed dose regimen of 4 units three times a week.[10 11] Consequently, the need for administration systems that allow for individualised daily dose schedules has become important to avoid wastage from either excessive hormone administration or incomplete vial usage. The multiple dose vial systems achieve that purpose, but do not greatly alter the convenience for the patient or care giver, except for the reduced frequency of vial preparation.

The child on hGH treatment is faced with daily injections for a number of years. Given the need to maintain sterility and for appropriate storage of the hormone and diluent vials, there are a number of practical inconveniences associated with classical formulations of hGH. These are perceived by many families as intrusive on their life styles. In addition the problems arising from the use of syringes and needles appear somewhat complex to families—this is seen in the present study among children 10 years or older who are far more likely to self administer hGH by Kabipen than syringe (table 1).

Little consideration has been previously given to the patient's attitudes in the choice of hGH delivery systems. We assessed in blind fashion the responses of 50 families who had experienced a syringe system before use of the injector pen. Most (92%) preferred the injector pen primarily because of the greater convenience. This included the considerably less time needed each day for hormone administration, the less complex preparation, the greater freedom to travel with less equipment, and a greater 'sense of independence'. These advantages were reflected in the increased frequency of self administration among pen users. Such autonomy facilitates the adaptation of the child to his/her treatment programme. Several families also expressed the concern that syringes and needles stored in the house could be taken and used for illicit drug use. The pen was also considered to be significantly more comfortable to use, although only a few (8%) gave this increased comfort as the primary reason for preferring the pen.

The reasons given by the small subgroup (8%) of subjects who preferred the syringe system principally included dissatisfaction regarding pen administration instruction and lack of information on and/or disappointment with growth progress. These concerns appear to be a reflection of inadequate information rather than any technical benefits that the syringe system had to the injector pen.

Very similar scores were given for the injector pen by those who had only used the injector pen and those who had used both systems. However, those who had used only the syringe systems tended to rate the syringe based systems better than those who had experience of both, reflecting that this was a group of older and longer treated patients, who had generally been reluctant to change systems and were generally satisfied with their management.

No difference in accuracy or recovery was observed between the two systems. However, the handling of the vial is minimal for the injector pen system assessed in this study. In contrast the handling of any syringe system will involve greater risk of error and of hormone loss or contamination. However, it should be noted that not all injector pen systems are equivalent. At least two other systems are marketed which require extensive handling of the hormone by the patient as the vial is not preloaded. As accuracy of dose delivery, hormone recovery, and cost are all equivalent in the systems we evaluated then the major consideration in the choice of a delivery system must be patient comfort. The present study clearly demonstrates patient preference for the injector pen delivery system.

The survey also clearly shows that the most successful way to educate patients and their families is to use a clinic nurse educator and/or a videotape.

In summary the Kabipen is an injector device that accurately delivers the dose set without any wastage from a 16 unit cartridge. When compared with syringe administration the Kabipen was clearly preferred by the majority of patients and was more likely to result in self administration in older children.

This work was funded in part by the Medical Research Council of New Zealand. We thank Ms Karen Tailuga and Vanessa Cox for their assistance.

1 Albertsson-Wikland K, Westphat O, Westgren U. Daily subcutaneous administration of human growth hormone in growth hormone deficient children. *Acta Paediatr Scand* 1986;75:89–97.

2 Kastrup KW, Sandahl Christiansen J, Koch Anderson J, Orskov H. Increased growth rate following transfer to daily s.c. administration from three weekly i.m. injections of hGH in growth hormone deficient children. *Acta Endocrinol (Copenh)* 1983;**104**:148–52.

3 Saubrey N, Arnold-Larsen S, Moller-Jensen B, Kuhl C. Comparison of continuous subcutaneous insulin infusion with multiple insulin injections using the novopen. *Diabetic Medicine* 1988;5:150–3.

4 Rosenfeld RG, Hintz RL, Johanson AJ, *et al.* Three year results of a randomised prospective trial of methionyl human growth hormone and oxandrolone in Turner syndrome. *J Pediatr* 1988;**113**:393–400.

5 Takano K, Shizume K, Hibi I. Turner syndrome: treatment of 203 patients with recombinant human growth hormone for one year. *Acta Endocrinol (Copenh)* 1989;**120**:559–68.

6 Wit JM, Fokker MH, de Muinck Keizer Schrama SM, *et al.* Effects of two years of methionyl growth hormone therapy in two dosage regimens in prepubertal children with short stature, subnormal growth rate and normal growth hormone response to secretagogues. *J Pediatr* 1989;**115**:720–5.

7 Koch VH, Lippe BM, Nelson PA, Boechat MI, Sherman BM, Fine RN. Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. *J Pediatr* 1989;**115**:365–71.

8 Stanhope R, Ackland F, Hamill G, Clayton J. Physiological growth hormone secretion and response to growth hormone treatment in children with short stature and intrauterine growth retardation. *Acta Paediatr Scand [Suppl]* 1989;**349**:47–52.

9 Smith PJ, Hindmarsh PC, Brook CG. Contribution of dose and frequency of administration to the therapeutic effect of growth hormone. *Arch Dis Child* 1988;**63**:491–4.

10 Preece MA, Tanner JM, Whitehouse RH, Cameron N. Dose dependence of growth response to human growth hormone in growth hormone deficiency. *J Clin Endocrinol Metab* 1975;**42**:477–83.

11 Frasier SD, Costin G, Lippe BM, Aceto T, Bunger PF. Dose response curve for human growth hormone. *J Clin Endocrinol Metab* 1981;**53**:1213–7.

MONATSSCHRIFT KINDERHEILKUNDE

139. Band Heft 3
März 1991

Organ der
Deutschen Gesellschaft
für Kinderheilkunde

Thema des Monats

Mukopolysaccharidosen
Editorial 119
M. Beck
Mukopolysaccharidosen: Nosologie – Klinik – Therapieansätze 120

Pädiatrie aktuell

Enterokokken als Sepsisursache bei Neu- und Frühgeborenen
Senkt die bereits vor der Schwangerschaft einsetzende Verbesserung der Stoffwechseleinstellung insulinabhängiger Diabetikerinnen das Risiko der Geburt fehlgebildeter Kinder?
Vergleich unterschiedlicher Immunglobulindosen bei der Behandlung des Kawasaki-Syndroms 128

Was hat das Kind?

Trainingsprogramm für die Weiterbildung zum Kinderarzt 129

Klinik und Forschung

S. Liptay, C. P. Bauer, A. Grübl, R. Franz, P. Emmrich
Atopieentwicklung in der frühen Kindheit – Prädisponierende Faktoren 130
Ch. Pabelick, B. Koletzko
Befunde bei Neugeborenen nierentransplantierter Mütter 136
W. Klapsch, Ch. Tschauner, R. Graf
Kostendämpfung durch die generelle sonographische Hüftvorsorgeuntersuchung 141
H. Bode, R. Bubl
Hirndurchblutung bei zerebralen Residualschäden. Eine Doppler-sonographische Studie 144

Der interessante Fall

U. Bertram, G. Hüls, W. Padberg, J. Turski, M. Altmannsberger
Entzündlich fibroider Polyp des Magens als ungewöhnliche Differentialdiagnose eines Oberbauchtumors 151
I. D. Mutz, R. Stering
Konnatales Neuroblastom und Plazentametastasen 154
W. Sperl, H. Fischer, J. Hager
Chilaiditi's Koloninterposition bei einer Patientin mit Rett-Syndrom 157
B. Sommer, H. L. Spohr
GM_2-Gangliosidose Variante 0 (M. Sandhoff): Verdachtsdiagnose einer Speicherkrankheit durch Ultraschall 160

Wußten Sie schon?

Aus der Klinik – für die Klinik
G. Conrad, A. Ch. Ludwig, F. Daschner
Sinnvolle und umweltschonende Desinfektion in der Pädiatrie 163
G. Conrad, M. Scherrer, F. Daschner
Vorschläge zur Abfallvermeidung und Umweltschutz in der Kinderklinik und kinderärztlichen Praxis 168

Was hat das Kind?

Auflösung und Kommentar des Trainingsprogramms 156

Tagesgeschichte 170
Tagungskalender 170

Abstracts der 21. Jahrestagung der Arbeitsgemeinschaft für Pädiatrische Nephrologie, 7.–9. 3. 1991 in Essen 174
Abstracts der 6. Jahrestagung der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung, 1.–4. 5. 1991 in Goldegg 189

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Hong Kong Barcelona Budapest

Annual subscription: DM 298,- plus postage

European Journal of
Pediatrics
Incorporating
Acta Paediatrica Belgica
and
Helvetica Paediatrica Acta

Volume 150 No. 5 1991

The pioneers of pediatric medicine
303

Review

Spontaneous pneumomediastinum in children
F. G. A. Versteegh, I. A. J. M. Broeders
304

Endocrinology

Persistent hyperthyrotropinaemia since the neonatal period in clinically euthyroid children
L. A. Tyfield, S. S. A. Abusrewil, S. R. Jones, D. C. L. Savage 308

Gastroenterology/Hepatology

Abnormal results of biochemical liver function tests in breast-fed infants with prolonged indirect hyperbilirubinaemia
Y. Tazawa, D. Abukawa, M. Watabe, M. Nakagawa, M. Yamada 310

Coombs-positive giant cell hepatitis of infancy: effect of steroids and azathioprine therapy
B. Brichard, E. Sokal, S. Gosseye, J. P. Buts, J. F. Gadisseux, G. Cornu
314

Hematology/Oncology

Malnutrition at diagnosis of malignancy in childhood: common but mostly missed
D. E. Smith, M. C. G. Stevens, I. W. Booth 318

Translocation t(8;16)(p11;p13) in neonatal acute monocytic leukaemia
T. Hanada, I. Ono, Y. Minosaki, N. Moriyama, S. Nakahara, A. Ohtsu
323

Immunology/Allergology

Autosomal recessive chronic granulomatous disease associated with 18q− syndrome and end-stage renal failure due to Henoch-Schönlein nephritis
J. Kimpen, R. Van Damme-Lombaerts, G. Van den Berghe, W. Proesmans
325

Anti-neutrophil antibodies in patients with nutritional copper deficiency
S. Higuchi, A. Higashi, T. Nakamura, Y. Yanabe, I. Matsuda 327

Infectious diseases

Tuberculosis in children: a 13-year follow up of 1714 patients in a Belgian home care centre
M. Toppet, A. Malfroot, B. Hofman, G. Casimir, F. Cantraine, I. Dab 331

Congenital cutaneous candidiasis: report of four cases and review of the literature
L. Almeida Santos, J. Beceiro, R. Hernandez, S. Salas, R. Escriba, E. Garcia Frias, J. Perez Rodriguez, J. Quero 336

Medical genetics

Reduced secretion of gastric inhibitory polypeptide in Turner patients with impaired glucose tolerance
E. Heinze, J. Schlickenrieder, R. W. Holl, R. Ebert 339

Calcinosis cutis, osteoma cutis, poikiloderma and skeletal abnormalities (COPS syndrome) – a new entity?
A. P. Oranje, S. M. P. F. de Muinck Keizer-Schrama, V. D. Vuzevski, M. Meradji 343

Metabolic diseases

A prevalent missence mutation in Northern Europe associated with hyperphenylalaninaemia
Y. Okano, R. C. Eisensmith, M. Dasovich, T. Wang, F. Güttler, S. L. C. Woo 347

N-Acetylglutamate synthetase deficiency: diagnosis, management and follow-up of a rare disorder of ammonia detoxication
G. Schubiger, C. Bachmann, P. Barben, J. P. Colombo, O. Tönz, D. Schüpbach 353

Neonatology

Combined conventional ventilation with high frequency oscillation in neonates
E. W. Hoskyns, A. D. Milner, I. E. Hopkin
357

Intraoperative measurements of cerebral haemodynamics during ductus arteriosus ligation in preterm infants
E. M. Saliba, A. Chantepie, F. Gold, M. Marchand, L. Pourcelot, J. Laugier
362

Aminophylline reduces cerebral blood flow in stable, preterm infants without affecting the visual evoked potential
O. Pryds, S. Schneider 366

Nephrology

A variant of nephrogenic diabetes insipidus: V_2 receptor abnormality restricted to the kidney
N. Knoers, L. A. H. Monnens 370

Haemostatic measurements in childhood nephrotic syndrome
A. T. H. Elidrissy, M. B. Abdurrahman, H. M. Bahakim, M. D. Jones, A. M. A. Gader 374

Indexed in *Current Contents*

Springer International

Subscription information

Volume 150 (12 issues) will appear in 1991. Information about obtaining back volumes and microform editions available upon request.

North America. Annual subscription rate: approx. US $ 1060.00 (single issue price approx. $ 102.00), including carriage charges. Subscriptions are entered with prepayment only.

Orders should be addressed to:

Springer-Verlag New York Inc.
Service Center Secaucus
44 Hartz Way
Secaucus, NJ 07094, USA
Tel. (201) 348-4033
Telex 023125994
FAX (201) 348-4505

All other countries. Annual subscription rate: DM 1598.00 plus carriage charges; Federal Republic of Germany: DM 27.61 incl. value added tax; all other countries: DM 60.60 except for the following countries to which SAL delivery (Surface Airmail Lifted) is mandatory: Japan DM 125.40, India DM 96.60, Australia/New Zealand DM 141.00. Airmail delivery to all other countries is available upon request. Volume price: DM 1598.00, single issue price: DM 159.80 plus carriage charges. Subscriptions can either be placed via a bookdealer or sent directly to:

Springer-Verlag
Heidelberger Platz 3, 1000 Berlin 33, FRG
Tel. (0)30/8207-0, Telex 183319
FAX (0)30/8214091

Archives of Disease in Childhood 1991; **66:** 689–692

Growth hormone treatment of growth failure secondary to total body irradiation and bone marrow transplantation

A Papadimitriou, M Uruena, G Hamill, R Stanhope, A D Leiper

Abstract

Growth hormone was given to 13 children (nine boys, four girls) with acute leukaemia who had undergone treatment with cyclophosphamide and total body irradiation before bone marrow transplantation. Mean age at total body irradiation and bone marrow transplantation was 9·0 years (range 3·7–15·8). Endocrinological investigation was carried out at a mean of 2·0 years (range 0·4–4·0) after bone marrow transplantation. Peak serum growth hormone responses to hypoglycaemia were <10·0 μg/l (<20·0 mU/l) in 10, 10·5 μg/l (21·0 mU/l) in one, >16·0 μg/l (>32·0 mU/l) in two patients. Mean age of the patients at the start of growth hormone treatment was 12·2 years (range 5·8–18·2). The mean time between total body irradiation and bone marrow transplantation and the start of growth hormone treatment was 3·2 years (range, 1·1–5·0). Height velocity SD score (SD) increased from a mean pretreatment value of −1·27 (0·65) to + 0·22 (0·81) in the first year, +0·16 (1·11) in the second year, and +0·42 (0·71) in the third year of treatment. Height SD score (SD) changed only slightly from −1·52 (0·42) to −1·50 (0·47) in the first year, to −1·50 (0·46) in the second year, and −1·74 (0·92) in the third year. Measurement of segmental proportions showed no significant increase in subischial leg length from −0·87 (0·67) to −0·63 (0·65) in the first year, to −0·58 (0·70) in the second year, and −0·80 (1·14) in the third year of treatment.

Our data indicate that children who have undergone total body irradiation and bone marrow transplantation respond to treatment with growth hormone in either of two dose regimens, with an increase in height velocity that is adequate to restore a normal growth rate but not to 'catch up', and that total body irradiation impairs not only spinal but also leg growth, possibly by a direct effect of irradiation on the epiphyses and soft tissues.

Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Department of Growth and Development
A Papadimitriou
M Uruena
G Hamill
R Stanhope

Department of Haematology and Oncology
A D Leiper

Correspondence to:
Dr Stanhope.

Accepted 22 January 1991

The introduction of high dose chemotherapy and radiotherapy with bone marrow transplantation to the armamentarium of treatments against malignant disease has made cure possible for a substantial number of children who would, hitherto, not have survived.[1] The high dose chemotherapy and total body irradiation that are used for conditioning such patients before bone marrow transplantation do, however, cause considerable morbidity; cataract formation,[1] gonadal failure, hypothyroidism, and growth failure have all been reported.[2 3] It has been suggested that total body irradiation impairs spinal growth,[2] and causes growth hormone insufficiency.[2 3] We have reported a 59% incidence of growth hormone insufficiency in children after bone marrow transplantation, some of whom had received cranial irradiation.[2] A high incidence of growth hormone insufficiency in children treated with total body irradiation has also been reported by Sanders *et al.*[3]

Children who have growth hormone insufficiency as a result of either cranial or craniospinal irradiation have an initial 'catch up' phase of growth in response to treatment with growth hormone, although it is less pronounced than that of children with idiopathic growth hormone deficiency.[4–7] This may be explained by the longer time for which children with congenital growth hormone deficiency have impaired growth hormone secretion, but all authors are agreed that both groups have a faster than normal growth rate (catch up) after starting growth hormone treatment.[4–7] We have analysed the short term effect of growth hormone treatment in 13 children treated with cyclosphosphamide, total body irradiation, and bone marrow transplantation for acute leukaemia.

Patients and methods

Thirteen patients (nine boys, four girls) who underwent bone marrow transplantation and total body irradiation for acute leukaemia and then received growth hormone treatment were included in this study. All had abnormal growth rates for their chronological age or stage of puberty, or both. The diagnosis was acute lymphoblastic leukaemia in 11 and acute myeloid leukaemia in two. Mean age at diagnosis was 6·5 years (range 0·5–14·1). All patients with lymphoblastic leukaemia had been treated for varying times with protocols established by the Medical Research Council,[8] the United Kingdom Children's Cancer Study Group,[9] or by the Hospital for Sick Children.[10] Patients with myeloid leukaemia were treated with daunorubicin, cytosine arabinoside, and thioguananine, or with two courses of this before one course of meta-amsacrine, azacytidine, and etoposide VP16 together with intrathecal cytosine arabinoside. Eight of those with lymphoblastic leukaemia had previously undergone cranial irradiation for the prevention of meningeal leukaemic infiltration in a dose of 1800 cGy (n=3) in 10 fractions over 12 days or 2400 cGy (n=5) in 15 fractions over 19 days. All the children with lymphoblastic disease also received intrathecal methotrexate. Eight patients had relapsed and were therefore given additional induction and consolidation chemotherapy before bone marrow transplantation. One boy (case 7) was also given treatment for testicular relapse with 2400 cGy testicular irradiation.

Allogeneic bone marrow transplantation was done during the first remission in five, the second remission in five, and the third remission in two patients. One patient underwent autologous bone marrow transplantation during the second remission after central nervous system relapse. Mean age at the time of treatment was 9·0 years (range 3·7–15·8). Preparation for marrow transplantation consisted of cyclophosphamide 60 mg/kg/day intravenously over two consecutive days and total body irradiation. The dose of irradiation was 900–1000 cGy given as a single fraction in 12 patients and in six fractions over three days in one.

A mean of 3·2 years (range 1·1–5·0) elapsed between irradiation and transplantation and the start of growth hormone treatment. The table gives the clinical data of 13 patients at the start of growth hormone treatment. The mean age of starting growth hormone treatment was 12·2 years (range 5·8–18·2). Endocrine replacement treatment was a standard regimen of hydrocortisone 15 $mg/m^2/day$ in two divided doses and thyroxine 100 $\mu g/m^2/day$. Human growth hormone treatment was started at a mean dose of 13·0 $U/m^2/week$ by daily subcutaneous injections and increased to a mean of 18 $U/m^2/week$ in the second and third years. Two patients (cases 9 and 13) had graft versus host disease, but only one (case 13) remained on steroid treatment while taking growth hormone. Statistical analysis was by paired Student's *t* test.

The endocrine status of all patients was assessed at a mean of 2·0 years (range 0·6–4·0) after total body irradiation and bone marrow transplantation. The hypothalamopituitary axis was tested with a combined provocative test using insulin, luteinising hormone releasing hormone, and thyrotrophin releasing hormone by standard techniques.[11] In four patients in whom growth hormone responded inadequately to hypoglycaemia (peak <10·0 μg/l (<20·0 mU/l)), a growth hormone releasing hormone test was done. Basal serum concentrations were also measured. After endocrine assessment patients were followed up clinically at three to six month intervals and repeat hormone measurements were made as necessary. Anthropometric measurements including standing and sitting height were assessed with stadiometers by standard techniques.[12] Pubertal stages were assessed by the method of Tanner.[13] Testicular volume after irradiation (localised irradiation as well as a component of total body irradiation) is an unreliable index of sexual maturity, so genital appearance was used.[14] Growth standards were those of Tanner *et al.*[15]

Results

ENDOCRINOLOGICAL INVESTIGATIONS

Serum growth hormone response to insulin induced hypoglycaemia was <10·0 μg/l (<20·0 mU/l) in 10 patients, six of whom had concentrations ≤5·0 μg/l (≤10·0 mU/l). One patient had a peak growth hormone of 10·5 μg/l (21·0 mU/l) and two had peak concentrations of >16·0 μg/l (>32·0 mU/l) (both had low growth velocities). Eight of the 10 patients with growth hormone insufficiency had been treated with cranial irradiation. Five out of the six patients with growth hormone concentrations <5·0 μg/l (<10·0 mU/l) had been treated with cranial irradiation (table). Only one of the four children who were tested with growth hormone releasing hormone had growth hormone concentrations higher than those achieved during insulin

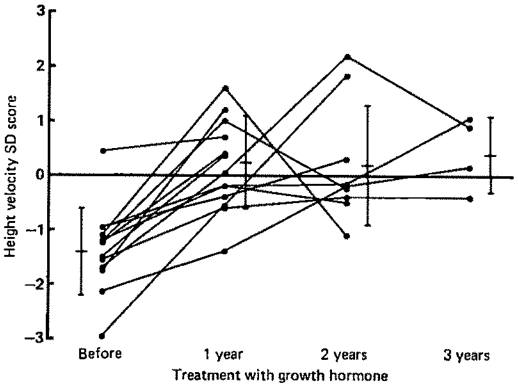


Figure 1 Height velocity SD scores at the beginning of growth hormone treatment, after 1 year (13 U/m²/week), and 2 and 3 years (18 U/m²/week) of growth hormone treatment in 13 children treated by total body irradiation and bone marrow transplantation.

Clinical and endocrine data of 13 patients treated with total body irradiation and bone marrow transplantation at the beginning of growth hormone treatment

Case No	*Sex*	*Previous cranial irradiation and dose (cGy)*	*Age at total body irradiation/ bone marrow transplantation (years)*	*Growth hormone peak to hypoglycaemia (μg/l)**	*Pubertal stage genitalia/breast*	*Endocrine replacement treatment*
1	M	2400	10·1	4·8	2	Nil
2	M	1800	5·4	7·5	1	Nil
3	M	1800	15·8	<0·3	4	Thyroxine
4	M	2400	5·1	5·0	1	Nil
5	F	Nil	6·5	9·9	1	Nil
6	F	2400	8·3	9·2	2	Oestrogen
7	M	2400 (2400 to testes)	11·1	1·1	1	Thyroxine, hydrocortisone
8	M	2400	9·8	5·6	4	Nil
9	M	Nil	12·2	10·5	3	Nil
10	F	Nil	9·7	>16·0	3	Oestrogen
11	M	Nil	12·0	>16·0	3	Thyroxine, testosterone
12	F	1800	3·7	3·3	1	Nil
13	M	Nil	7·3	4·5	1	Thyroxine, hydrocortisone

All patients had acute lymphoblastic leukaemia except numbers 5 and 11 who had acute myeloid leukaemia.
*Growth hormone conversion: 1 μg/l=2 mU/l.

induced hypoglycaemia, but none achieved values >10·0 μg/l (>20·0 mU/l).

Four patients were hypothyroid (cases 3, 7, 11, and 13) at the time of the initial investigation, case 2 had compensated hypothyroidism identified by persistently raised concentrations of thyroid stimulating hormone (>10·0 mU/l). All four were treated with thyroxine as were two patients (cases 1 and 8) who became hypothyroid 3·7 and 2·5 years later, respectively. Adrenal function was considered normal in all patients except two (cases 7 and 13), who subsequently received hydrocortisone replacement for panhypopituitarism. During the study, sex steroid replacements were given to six patients. Three patients (cases 6, 7, and 10) had increased serum concentrations of follicle stimulating hormone and luteinising hormone on investigation; two (cases 1 and 8) had arrested pubertal development and one (case 13) delayed puberty. Patients less than 10 years of age at investigation did not have raised gonadotrophin concentrations, although at this age it is impossible to exclude gonadal damage by measurement of serum gonadotrophins.

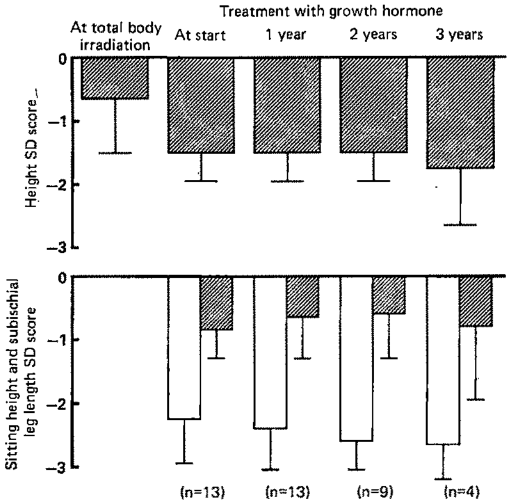


Figure 2 Height, sitting height, and subischial leg length (shaded columns) SD scores before and during growth hormone treatment in 13 children treated by total body irradiation and bone marrow transplantation.

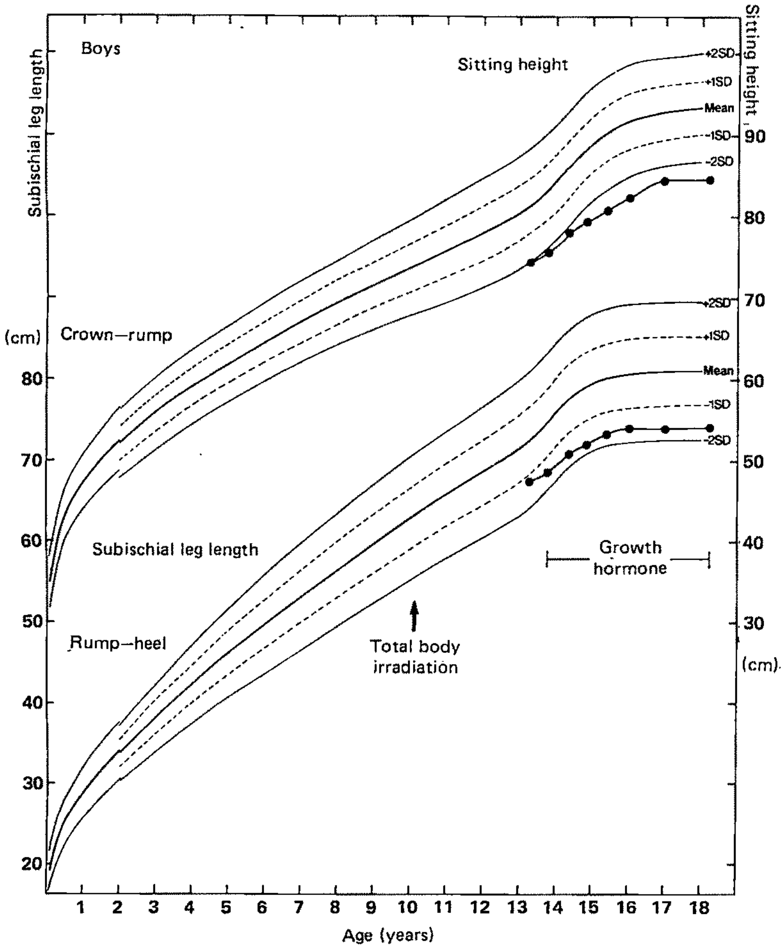


Figure 3 Sitting height and subischial leg length response to treatment with growth hormone in case 1 until the attainment of adult stature. Epiphyseal maturation was one year behind chronological age at the start of treatment. He had been treated with 2400 cGy cranial irradiation at the age of 3·8 years and total body irradiation was given at the age of 10·1 years. He had spontaneous onset of pubertal development at age of 13·2 years but sex steroid supplements were given at the age of 15·1 years for arrested sexual maturation.

GROWTH IN RESPONSE TO TREATMENT WITH GROWTH HORMONE

In the first year of growth hormone treatment all patients increased their growth velocity, expressed as height velocity SD score (SD), from a mean of −1·27 (0·65) in the year before treatment to +0·22 (0·81), ($p<0·001$) (fig 1). During the second year of treatment the mean height velocity SD score was +0·16 (1·11) and during the third year it was 0·42 (0·71). Height velocity SD score did not rise significantly above zero in any year of treatment, showing that these patients did not experience 'catch up' growth. Expressing growth velocity in cm/year (SD) in the first year of treatment, patients increased their height velocity from a mean value in the year before treatment of 3·6 (0·95) cm/yr to 5·2 (1·5), whereas in the second year it decreased to a mean of 5·0 (2·5) cm/year, and in the third year to 4·6 (2·0) cm/year.

Mean height SD score at the time of bone marrow transplantation was −0·66 (0·84) and when growth hormone treatment started it decreased to −1·52 (0·42) ($p<0·05$). Growth hormone treatment did not result in improvement of height SD scores (fig 2); during the first year there was a slight increase to a mean value of −1·50 (0·47), which was maintained in the second year at −1·5 (0·46), and then decreased to −1·74 (0·92) in the third year.

The response of body segments to growth hormone treatment are shown in fig 2. At the start of growth hormone treatment, sitting height SD scores (SD) had been affected more than subischial leg length, with a mean value of −2·26 (0·68) and −0·87 (0·63), respectively. During treatment there was a progressive, although not significant, decrease in mean sitting height SD scores, from −2·46 (0·64) in the first year, to −2·60 (0·50) in the second year, and −2·66 (0·59) in the third year. The response of subischial leg length to growth hormone treatment was also not significant: in the first year mean subischial leg length SD score was −0·63 (0·65), in the second year −0·58 (0·70), and in the third year −0·8 (1·14). An example of impaired sitting height and subischial leg length responses to growth hormone treatment is shown in fig 3 (case 1).

Discussion

The patients in this study are a heterogenous group because of their wide age range, differing pubertal state, and varying numbers of previous remissions and irradiation regimens. They were, however, treated at a time when total body irradiation and bone marrow transplantation were first used in our unit, and before this such children would not have been expected to survive. Growth assessment and potential may be complicated by chronic corticosteroid treatment in those patients with severe graft versus host disease, but only one of our patients was on pharmacological corticosteroid treatment during growth hormone treatment. We have previously shown that growth hormone insufficiency is a common result of total body irradiation and this is especially true for children who have been treated with bone marrow transplantation during their second or third remission and have already received cranial irradiation.[2] We can offer no explanation as to why sitting height SD scores were much lower than subischial leg length SD scores before growth hormone treatment.

Children who do not produce enough growth hormone as a result of cranial or craniospinal irradiation have been reported to respond to growth hormone treatment with an initial catch up growth period, although this is not as pronounced as in those children with idiopathic growth hormone deficiency.[4–7] In this study patients showed an increase in height velocity adequate for growth at a normal rate for age (height SD scores increased from a minus number to zero), but this was not catch up growth (height SD scores were not significantly above zero). Children with idiopathic growth hormone deficiency have catch up growth in response to growth hormone treatment with doses similar to that used in the first year for our patients.[16] We provided a higher dose in the second and third years but with no further improvement in growth response. It is possible that higher doses of growth hormone, such as those used now in the treatment of dysmorphic syndromes (30 U/m^2/week), may be needed for optimal growth of such children.

Impaired spinal growth despite growth hormone treatment was expected in our patients, as growth hormone does not reverse impaired growth of the spine in children who have undergone craniospinal irradiation.[17] It was recently reported that children treated with only cranial irradiation also had abnormal unexplained spinal growth, but the data are from a small number of patients.[18] The patients in our study had impaired leg growth while on growth hormone treatment even though they received full endocrine replacement, suggesting that total body irradiation impaired the growth of both lower limb and vertebral epiphyses. Irradiation of the bones of the legs impairs the growth of the lower limbs,[19] [20] just as spinal irradiation affects the growth of the vertebral bodies.[21] As growth failure in these children was more pronounced than expected for such a low total dose of irradiation, it may be attributable to the effect of total body irradiation given as a single fraction in almost all the patients. It is possible that fractionation of the dose will decrease the adverse effects on growth as well as other complications.

Children treated with total body irradiation and bone marrow transplantation have profound growth failure, which is only partially the result of endocrine deficiency. They have impaired response to growth hormone treatment in the lower segment of the body as well as in the spine, which is probably secondary to irradiation of the epiphyses. Such damage may be irreversible and this emphasises that children who have been treated with total body irradiation and have growth failure require endocrine replacement as soon as possible to maximise their impaired growth potential.

Dr Leiper is supported by a grant from the Medical Research Council. We are grateful to Professor JM Chessells for her encouragement and constructive criticism of the manuscript.

1 Deeg HJ. Bone marrow transplantation: a review of delayed complications. *Br J Haematol* 1984;57:185–208.

2 Leiper AD, Stanhope R, Lau T, *et al.* The effect of total body irradiation and bone marrow transplantation during childhood and adolescence on growth and endocrine function. *Br J Haematol* 1987;67:419–26.

3 Sanders JE, Pritchard S, Mahoney P, *et al.* Growth and development following marrow transplantation for leukemia. *Blood* 1986;68:1129–35.

4 Shalet SM, Whitehead C, Chapman AJ, Beardwell CG. The effects of growth hormone therapy in children with radiation-induced growth hormone deficiency. *Acta Paediatr Scand* 1981;70:81–6.

5 Cowell CT, Quigley CA, Moore B, *et al.* Growth and growth hormone therapy of children treated for leukaemia. *Acta Paediatr Scand* 1988;343(suppl):152–61.

6 Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following craniospinal irradiation. *Eur J Pediatr* 1988;147:597–601.

7 Lannering B, Marky J, Mellavder L, Albertsson-Wikland K. Growth hormone secretion and response to growth hormone therapy after treatment for brain tumour. *Acta Paediatr Scand* 1988;343(suppl):146–51.

8 Chessells JM, Ninane J, Tiedeman K. Present problems in management of childhood lymphoblastic leukaemia. Experience from Hospital for Sick Children. In: Neth R, Gallo RC, Graaf T, Mannweiler R, eds. *Modern trends in human leukaemia IV.* Berlin: Springer, 1981:108–14.

9 Mott MG, Chessells JM, Willoughby MLN, *et al.* Adjuvant low dose radiation in childhood T-cell leukaemia/lymphoma (report from the United Kingdom Children's Cancer Study Group–UKCCSG). *Br J Cancer* 1984;50: 457–62.

10 Chessells JM, Leiper AD, Tiedeman K, Hardisty RM. Oral methotrexate is as effective as intramuscular methotrexate in maintenance therapy of acute lymphoblastic leukaemia. *Arch Dis Child* 1987;62:172–6.

11 Hughes IA. *Handbook of endocrine tests in children.* Bristol: Wright, 1986.

12 Brook CGD. *Growth assessment in childhood and adolescence.* Oxford: Blackwell, 1982.

13 Tanner JM. *Growth at adolescence.* 2nd Ed. Oxford: Blackwell, 1962.

14 Leiper AD, Grant DB, Chessells JM. Gonadal function after testicular radiation for acute lymphoblastic leukaemia. *Arch Dis Child* 1986;61:53–6.

15 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity, British children 1965. *Arch Dis Child* 1966; 41:613–5.

16 Milner RDG. Proper use of growth hormone. *Arch Dis Child* 1990;65:70–1.

17 Shalet SM, Clayton PE, Price DA. Growth impairment following treatment for childhood brain tumours. *Acta Paediatr Scand* 1988;343(suppl):137–45.

18 Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following cranial irradiation. *Eur J Pediatr* 1988;147:593–6.

19 Probert JC, Parker BR. The effects of radiation therapy on bone growth. *Radiology* 1975;114:155–62.

20 Vaughan JM. *The effects of irradiation on the skeleton.* Oxford: Clarendon Press, 1973:83–8.

21 Probert JC, Parker BR, Kaplan HS. Growth retardation in children after megalovoltage irradiation of the spine. *Cancer* 1973;32:634–9.

Archives of Disease in Childhood 1991; **66:** 693–695

Asperger's syndrome: who is being abused?

M Perkins, S N Wolkind

Abstract

Six case histories of children referred and admitted to a psychiatric inpatient unit at a tertiary referral centre because of concerns about poor functioning and possible emotional abuse are presented. On initial assessment the children appeared to be well functioning and the impression was confirmed that their emotional needs were not being met by their parents. After detailed inpatient appraisal the diagnosis of Asperger's syndrome was made in all six cases, exemplified mainly by a formal concrete way of thinking and an inability to identify and understand human emotions and relationships. The impact of the diagnosis on the parents and their consequent relationships with their child and their willingness to work with professionals is discussed.

Since Kanner's clinical account of 1943 there has been a growing interest in the pervasive developmental disorders of children, of which autism is the most well defined.[1] Rutter has most clearly set out the current basic requirements for the diagnosis of this condition.[2] Firstly, the onset of developmental impairment should be within the first 30 months of life. Secondly, there is a deviance of social relationships. Those that are formed are not appropriate to the child's mental age. Thirdly, autistic children have a wide range of abnormalities of communication. Fourthly, there are restricted, repetitive, stereotyped patterns of behaviour. In its classical form it is now readily recognised by experienced professionals.

More recently milder forms of these disorders have been described. Asperger's syndrome provides an example of this and Wing has delineated the characteristics of this condition.[3] The affected individuals show a lack of empathy and have deviant styles of both verbal and nonverbal communication. They may embark upon long pedantic monologues on certain topics, with little emotional expression. They have constricted intellectual interests which may be to the exclusion of all else. Finally, they may show idiosyncratic attachment to inanimate objects. There are continuing debates as to whether these conditions are truly mild forms of autism or of some other type of disorder such as an early manifestation of schizoid personality.[4 5] Whatever the answer to this the prognosis of these children is poor and the majority will, as adults, have major psychosocial difficulties.

These latter disorders are not common and they can be difficult for professionals to recognise. During a clincal interview the children can appear sociable and at times even desperate to form a relationship with the interviewer. Doctors and psychologists can fail to understand how emotionally draining it is to bring up such a child. The parents can be made to feel increasingly guilty that they have failed to meet their children's needs and may be blamed for difficulties that have been observed at school. A previous theory, now totally refuted,[6] was that abnormalities in parenting were the direct cause of autism and the other developmental disorders. It is, however, almost certain that the cause is due to some form of brain dysfunction probably with a genetic basis,[7] and indeed similar difficulties are often seen in other family members.

Over the last two years six children with Asperger's syndrome have been seen in a tertiary referral centre where previous workers have felt either the parents were fabricating the difficulties or that the children's behaviour was the result of emotional or sexual abuse. Only after admission did the nature of the behavioural abnormalities become clear. In most cases the parents' behaviour appeared at initial assessment to be either hostile, defensive, or even bizarre. Only as staff became able to empathise with their frustration at trying to cope with their child did their despair and isolation become apparent. A case history is presented of one such child and family and a table gives details of the remaining five.

Case report

A girl (case 1) was referred aged 10. Owing to her father's work the family had lived abroad a great deal. From age 18 months the mother had felt there was 'something wrong' with the girl, her first child. 'She never seemed to be really present: she didn't play like other children'. The worries grew when she compared her with her brother two years younger. The mother's fears were dismissed as 'neurotic' by a company doctor. At age 5 she started school; she was thought odd at the time and the term 'a rejected child' was used. An educational psychologist assessed her as having an intelligence quotient (IQ) of 85 and agreed with teachers that 'under an aloof exterior this was a child desperate for love'. The parents considered having psychiatric treatment for themselves. The father declined a promotion so that he could spend more time with the family. When the girl was aged 8, a third child was born and the mother was concerned that the girl might harm the new baby. Both the general practitioner and the health visitor felt the girl had a normal interest in her

Maudsley and Bethlem Royal Hospitals, Denmark Hill, London SE5 8AZ
M Perkins
S N Wolkind

Correspondence to:
Dr Wolkind.

Accepted 14 January 1991

Details of the six children

Case No/sex	*Intellectual quotient*	*Neurological deficit*	*Development difficulties*	*Social difficulties (child)*	*Parental history*	*Social difficulties (parents)*
1/F	Full scale 60,* performance 64, verbal 60	EEG: normal, computed tomogram: slightly enlarged ventricles	Language delay, spelling difficulties	Indiscriminate approaches to adults. No concept of friendship. Preoccupation with violence to babies	Father: managerial post, mother: housewife	Warm, appropriate care of other children
2/M	Full scale 84, performance 101, verbal 72	EEG: generalised dysfunctional types non-specific. 'Clumsy'	Limited symbolic play	Indiscriminate approaches to adults. No concept of interactive play. Pronounced obsessional traits	Father: self employed butcher, mother: housewife	Recurrent depressive illness in mother
3/M	Full scale 77, performance 78, verbal 79	EEG: normal, computed tomogram: normal	Visual and peripheral memory deficit	No concept of friendships. No concept of interactive play. Preoccupation with fungi/insects	Father: self employed shop owner, mother: housewife	Marital discord. Mother withdrawn, lacking friends and socially isolated
4/F	Full scale 71, performance 71, verbal 67	No neurological deficits	Non-reader	Indiscriminate relationship with adults. No concept of friendship. No concept of play	Father: car mechanic, mother: housewife	Father passive, suffered depression. Mother cold, affectionless with institutional up bringing
5/M	Full scale 89, performance 87, verbal 94	EEG: normal, computed tomogram: normal	Language delay	No concept of friendship. No imaginative play. Preoccupation with ritualistic drawing	Father: manual worker, mother: housewife	Father rubber fetishist. Solitary, isolated individual, pronounced sexual fetishist. Preoccupation with trains
6/M	Full scale 138, performance 130, verbal 137	EEG: normal	None	No concept of friendship. Preoccupation with orderliness	Father: sales representative, mother: shop assistant	Father socially isolated. Mother withdrawn with history of drug/alcohol abuse

*Please note discrepancy in quoted IQ scores which led to much investigation for organic brain deterioration, which was not later substantiated. EEG, electroencephalogram.

new sister. A total lack of educational progress led to a full assessment under the 1981 Education Act. The parents obtained a psychiatric opinion and referral to a child psychiatry inpatient unit was recommended.

On admission, she was a pale child and small for her age. On first contact she appeared to be highly sociable and well able to deal with social situations. She appeared to show a full range of normal emotions. It became readily apparent that these were learned behaviours and had no feeling or flexibility behind them. She had no concept of humour or of empathy. Her language in new situations was restricted and formal. Free play showed an obsession with babies and she would muse in a cold detached way about methods of killing them. Physical examination showed her height and weight on the 10th centile but no other abnormalities. A computed tomogram showed slightly enlarge ventricles but an electroencephalogram was normal. These features suggested Asperger's syndrome and it was thought that her apparent good social functioning was due to the enormous efforts made by her parents in their attempts to relate to her and enable her to cope with society. It was also thought that she had a definite potential of violence towards babies and a boarding school placement was recommended. Much work was needed to restore the parents' self esteem and to ensure that they would continue to offer all they could to their daughter.

Brief details of all six children are shown in the table. It can be seen that four of the six children were boys, a proportion that reflects the general excess of males with developmental disorders. All the children showed some evidence of impairment in the three main areas. In social abnormalities the majority showed a complete inability to understand other's feelings and had no concept of the meaning of abstract notions such as friendship or love. The communication difficulties ranged from a moderately stilted form of speech to grossly formalised almost robotic ways of communicating. The abnormal preoccupations ranged from an excessive amount of time being spent with a collection of toy cars to a child whose total day at school and at home was dominated by a preoccupation with fungi and the poisons that could be obtained from them (case 4). In all cases at least one professional with the power to make decisions affecting the child's life had formally recorded suspicions of abuse by the parents.

Discussion

These six cases shared many features. A superficial knowledge of each of the children would suggest a well functioning child whose emotional needs were somehow not being fully met. It required the experience of seeing the child in an inpatient unit before the full nature of the children's difficulties became apparent. Within days, staff would change their view from puzzlement at how the parents could complain about such a child to exasperation as the repetitive unrewarding nature of the interactions undermined the attempts by nursing staff to get to know their new patient. The parents had all been overwhelmed by guilt. They had all suggested that something had been very wrong but in all cases this had been dismissed by at least some of the professionals who had seen them. Three of the parents had considered that their child might be autistic and had read a great deal about the nature of the disorder. The unusual nature of their children's personalities and the feeling of an outsider or an observer living in the family led to extreme distress and parental behaviours that at times would appear bizarre. They had become very defensive towards professionals and suspicious in their dealings with them. In only one case did a parent have a history suggesting a full Asperger's syndrome, but he had played no part in caring for the child.

The key features the children demonstrated were a formal concrete way of thinking and an inability to identify and understand human emotions and relationships. Two of the children had worrying preoccupations with violence and death. In all cases the parents or foster parents were immensely relieved when a formal diagnosis was given to them even though they appreciated its prognostic significance. When their longstanding anxieties were acknowledged, all became willing and keen to work with staff for the good of their children. These histories point to the need to make formal mental state examinations of children. Four of the six had been seen previously by mental health professionals who had focused on family dynamics. Though these are of great importance they are not a substitute for a full psychiatric evaluation. With growing acceptance of the important concept of emotional abuse, in all these cases accusations that this was the cause of the problem had been made. In three cases formal case conferences had been held.

Despite these comments, children with even the most severe personality and developmental deviations can and do get abused emotionally, physically, and sexually. In any assessment of a non-functioning child the evaluation must include both family and social experiences and the child's own individual development and psychopathology. The milder forms of autism need to be recognised early so that parents can be helped to handle their unusual child and so that preventative work can be undertaken to stop severe behavioural problems being added to the underlying difficulty.

1 Kanner L. Autistic disturbance of affective contact. *Nervous Child* 2:217–50.

2 Rutter M. Diagnosis and definition of childhood autism. *J Autism Dev Disord* 1978;8:139–61.

3 Wing L. Asperger's syndrome: a clinical account. *Psychol Med* 1981;11:115–29.

4 Wolff S, Barlow A. Schizoid personality in childhood: a comparative study of schizoid, autistic and normal children. *J Child Psychol Psychiatry* 1979;20:29–46.

5 Wolff S, Urich J. Schizoid personality in childhood a controlled follow-up study. *Psychol Med* 1980;10:85–100.

6 Cantwell DP, Baker L, Rutter M. Family factors. In: Rutter M, Schopler E, eds. *Autism: a reappraisal of concepts and treatment*. New York: Plenum Press, 1978.

7 Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry* 1977;18:297–321.

Brothers and sisters and the management of cerebral palsy

Brothers and sisters are important. That the relationships between a handicapped child and his or her brothers and sisters may have important consequences seems self evident. Workers in Iowa (Martha Craft and colleagues, *Developmental Medicine and Child Neurology* 1990;**32**:1049–57) have tried to assess the effects of teaching siblings of children with cerebral palsy. They studied 15 children who had cerebral palsy and 16 normal siblings aged between 4 and 17 years. The normal siblings underwent a four month programme of education about the basic neurology of cerebral palsy and about motivational skills and ways of encouraging more independence in the handicapped child, the teaching being appropriate to the age of the sibling. After the programme the cerebral palsied children had increased ranges of movement in the joints of the upper limbs. Measures of self help skills showed no significant change, although the authors point to a 'trend' towards improvement and state that 'a few increases in functional status were dramatic'.

My enthusiasm for this work is cautious. Scientific assessment of management in cerebral palsy is notoriously difficult and anybody who tries it is to be encouraged. This study, however, is uncontrolled and the authors' enthusiasm for their own work is evident from their writing. They have shown some increase in joint mobility but no significant change in functional capacity. Reports of apparently dramatic changes in some patients are difficult to assess and can be produced by the practitioners of even the most obscure alternative therapies. It worries me too that they appear to give little consideration to the effect on the normal siblings. Their age range was wide and the implication seems to be that they all entered into things in a spirit of sibling love and altruism. Did none of them react against it or just get fed up? What will be the long term effects? It is important to avoid cynicism while at the same time preserving professionally detached judgment and trying to assess the validity and implications of the work. I'd like more information.

ARCHIVIST

Archives of Disease in Childhood 1991; 66: 696–697

Management of foreskin problems

P M Lafferty, F B MacGregor, W G Scobie

Abstract

One hundred consecutive cases of boys with foreskin problems referred to local paediatric surgeons in the Edinburgh area were studied. Fifty five underwent circumcision and the remainder were managed more conservatively with or without the use of local or general anaesthetic. Although sometimes avoiding general anaesthetic, the more conservative methods involved more frequent visits to the clinic, a larger number of complications, and a longer follow up period.

Despite the vogue for conservatism, circumcision still has an important part to play in the management of troublesome foreskins in children.

Circumcision is a very old and widely practised surgical procedure. Today, in many countries such as the United States, the decision to circumcise is made by the parents. A recent report revealed that the most important factor associated with the decision to circumcise was whether or not the father was circumcised.[1] This routine practice continues despite policy statements by the American Academy of Pediatrics and the American College of Obstetrics and Gynecology.[2]

Neonatal circumcision is not a routine procedure in the United Kingdom, but a large number of infants and school age boys are referred to surgical paediatric departments with foreskin problems for possible circumcision.

The presenting complaints vary from individual to individual. Most frequently symptoms appear related to degrees of tightness of the foreskin:from overt phimosis associated with a pin hole meatus to failure to fully retract the foreskin due to congenital adhesions remaining between the glans and foreskin. Extreme phimosis may impede urinary flow, the small voiding orifice causing the foreskin to balloon during micturition.

Localised infection and inflammation together constitute a common cause for referral with foreskin problems, either alone or together with symptoms of phimosis. Balanitis (inflammation of the glans) although often quoted as a major presenting complaint, is in fact much less common than posthitis (inflammation of the foreskin). Retention of smegma, together with the gradual breakdown of congenital adhesions may significantly contribute to localised irritation and inflammation in and around the foreskin as it gradually softens and dilates, allowing full retraction usually by the fifth or sixth year.

Renewed interest in conservation of the foreskin and the advent of topical anaesthetic creams, such as Emla (eutectic mixture of local anaesthetics (lignocaine and prilocaine), Astra),[3] has prompted a prospective analysis of methods of management in the Edinburgh area.

Patients and methods

One hundred consecutive patients with foreskin problems, referred to the two Edinburgh paediatric surgical units (the Royal Hospital for Sick Children and the Western General Hospital) were analysed over a six month period. All children referred were seen by one of four consultant paediatric surgeons or a career senior registrar. A proforma was completed at the initial consultation that recorded the patient's details, reasons for referral, and the treatment implemented. All operative procedures, including Emla lysis, were performed by the full range of medical staff, from consultant to senior house officer.

Follow up was to patient discharge. Statistical analysis of figures was achieved by one way analysis of variance and Mann-Whitney tests.

Results

Reasons for referral are shown in table 1. The most common reasons for referral as witnessed by the referring letter or the parental history related to tightness of the foreskin and/or recurrent infection. Where phimosis was apparent it was categorised by the attending surgeon as either pin hole (n=54) or meatus visible (n=46). Only 8% of referrals requested circumcision on religious grounds. Four patients required no treatment and were discharged.

The basis on which the decision to adopt either surgical or conservative treatment was made ultimately on personal preference of the attendant surgeon. Recurrent infection, pin hole meatus associated with ballooning on micturition, and failed conservative management, however, were regarded as relative indications for circumcision. Forty nine patients had circumcision performed after their initial visit to the clinic.

Table 1 Presenting complaints in 100 consecutive cases

	No of patients
Phimosis	49
Infection	39
Ballooning	17
Failure to retract	24
Religion	8
Parental request	0

Some boys had more than one presenting complaint.

Paediatric Surgical Department, Western General Hospital, Edinburgh
P M Lafferty
W G Scobie

Ear, Nose, and Throat Department, City Hospital, Edinburgh
F B MacGregor

Correspondence to:
Mr P M Lafferty,
Gastrointestinal Laboratories,
Western General Hospital,
Crewe Road,
Edinburgh EH4 2XU.

Accepted 30 January 1991

Persistent preputial adhesions or failure to fully retract the foreskin (both with and without significant phimosis) attracted a largely conservative approach with 13 patients undergoing Emla lysis (as outlined by MacKinlay[3]) and 26 undergoing preputial stretch/adhesion lysis under general anaesthesia.

In eight patients in whom the symptoms were of minimal persistent adhesions only, an expectant policy was adopted; this involved gentle foreskin retraction being taught to the parents and practised at home. Not surprisingly in this latter group, in whom the symptoms were very mild, there were no complications. The mean number of total hospital visits, including the first, were recorded and are shown in table 2.

Those in the Emla group visited the department 2·9 times on average. Those undergoing preputial stretch and circumcision visited a mean of 3·4 and 2·8 times respectively. Comparing all three groups, there was an overall statistical difference between the mean number of hospital visits (analysis of variance, $p<0·005$). A highly significant difference occurred between the preputial stretch/adhesion lysis group and circumcision groups (Mann-Whitney test, $p=0·0006$). There was no significant difference between the mean number of hospital visits in the Emla lysis and circumcision groups. It is noted however that the practice at the Royal Hospital for Sick Children was to carry out Emla lysis, if indicated, at the initial visit, thus decreasing the number of attendances. At the same unit, follow up of circumcisions was often carried out by the district nurse, again decreasing the number of hospital attendances.

Two of the 13 boys (15%) in the Emla group continued to have problems resulting in subsequent circumcision (table 3). Of the 26 boys who underwent preputial stretch, seven (27%) reported persisting problems of these four proceeded to circumcision and one had a further preputial stretch, all of which required general anaesthesia. Of the 49 boys who underwent circumcision as initial treatment, only four (8%) reported problems and none required further operative treatment.

Table 2 Total numbers of hospital visits (including the first)

	No of patients	*Mean No visits/ patient (range)*
Emla lysis	13	2·9 (2–5)
Preputial stretch	26	3·4 (2–5)
Circumcision	49	2·8 (2–4)

Table 3 Complications

	No of patients	*No (%) of complications*	*Action*
Emla lysis	13	2 (15)	
		Residual adhesions	Circumcision
Preputial stretch	26	7 (27)	
		Persistent ballooning (n=1)	None
		Residual adhesions (n=1)	None
		Recurrent phimosis (n=4)	Circumcision
		Repeated infection (n=1)	Preputial stretch
Circumcision	49	4 (8)	
		Crusting/bleeding	None

Discussion

Forty nine of 100 boys referred by their family doctors to two sister paediatric surgical units in Edinburgh had circumcision as the primary management of the presenting foreskin problem. A further six patients underwent circumcision after failure of foreskin preserving measures which included preputial stretch/adhesion lysis under general or local (Emla) anaesthetic. The remainder were managed by more conservative methods, with or without local or general anaesthetic. Only a small number of circumcisions were carried out for religious reasons in the Edinburgh area where the population of ethnic minorities is small.

Emla cream has proved to be useful for local anaesthesia before adhesion lysis in selected, compliant patients. In addition, it is recognised that this method is appropriate for those boys with persistent preputial adhesions but not for those with any significant degree of phimosis.[3]

A complication rate of 27% after preputial stretch/adhesion lysis is noted; five of the seven boys with continuing symptoms were noted to have 'pin hole meatus' at the first visit. This indicated a need for improved patient selection in this particular treatment group.

Surveys have shown that the uncircumcised child has a higher risk of foreskin/glanular problems compared with the circumcised child (14·0% *v* 6·0% and 18·8% *v* 11·1%).[4 5] Stenram *et al* showed that meatal stenosis occurred in up to 11% of boys after circumcision.[6] The argument against circumcision because of the risks of general anaesthesia are now less relevant with the advent of safer anaesthetic agents, paediatric trained anaesthetics, and modern monitoring equipment.

Although conservatism is now the mode in foreskin problems, it often increases the number of hospital attendances, and had a higher complication rate in this series.

The authors would like to thank Mr W Bissett, Mr G MacKinlay, and Mr J Orr for allowing us to report their patients in this study.

1 Brown MS, Brown CA. Circumcision decision: prominence of social concerns. *Pediatrics* 1987;**80**:215–9.
2 Evanston IL. *Guidelines for perinatal care*. American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 1983:87.
3 MacKinlay GA. Save the prepuce. Painless separation of preputial adhesions in the out-patient department. *BMJ* 1988;**297**:590–1.
4 Herzog LW, Alvarez SR. The frequency of foreskin problems in uncircumcised children. *Am J Dis Child* 1986; **140**:254–6.
5 Fergusson DM, Lawton JM, Shannon FT. Neonatal circumcision and penile problems: an eight year longitudinal study. *Pediatrics* 1988;**81**:537–41.
6 Stenram A, Malmfors G, Okmian L. Circumcision for phimosis: indications and results. *Acta Paediatr Scand* 1986;**75**:321–3.

Archives of Disease in Childhood 1991; **66:** 698–701

Prevalence of liver disease in cystic fibrosis

R Scott-Jupp, M Lama, M S Tanner

University of Leicester,
Deparment of
Child Health,
Clinical Sciences
Building,
Leicester Royal
Infirmary,
POB 65,
Leicester LE2 7LX
R Scott-Jupp
M Lama
M S Tanner

Correspondence to:
Dr Scott-Jupp.

Accepted 21 January 1991

Abstract

To assess the prevalence, demography, and clinical features of liver disease among patients with cystic fibrosis the case notes of 524 patients of all ages who were attending the cystic fibrosis clinic were studied. Computer databases were used to establish the condition of the liver in a further 576 such patients. The overall prevalence of overt liver disease indicated by the presence of an enlarged liver or spleen (or both) was 4·2%. The age related prevalence rose to a peak in adolescence, and then fell in patients over 20 years old. The implied increase in mortality among those with liver disease was not explained by deaths from liver disease, which were rare. Male patients were significantly more affected than female, the ratio being 3:1 among adolescents. Increasing prevalence of liver disease in patients with cystic fibrosis is, therefore, not just a result of longevity.

Liver cirrhosis was recognised as a complication of cystic fibrosis in Andersen's original description in 1938, but until recently the importance of subclinical liver disease has been eclipsed by the more obvious respiratory and pancreatic signs and symptoms.[1] More effective management of these has resulted in greatly improved survival, and so liver disease has become important to a larger number of patients.

The aetiology of focal biliary cirrhosis in cystic fibrosis is uncertain,[3] but poor nutrition,[4] inspissated bile,[5] autoimmunity,[6] and biliary tract obstruction[7 8] have all been suggested.

Previous estimates of prevalence varied depending on the diagnostic criteria used.[9 10] If cross sectional necropsy data are combined it looks as if prevalence rises steadily with age.[5 11 12] There has been no study of clinically important liver disease in a large group of patients with cystic fibrosis spanning the entire age range.

A number of authors have shown that liver function tests are disordered in a high proportion of patients with cystic fibrosis and liver impairment, but that the degree of abnormality does not correlate with the extent of cirrhosis.[5 13–16] Some patients with obvious liver disease have normal test results, and there is a large number whose results are abnormal and whose true liver condition is uncertain.[9 10]

Patients and methods

The casenotes of all 524 patients attending adult and paediatric specialist cystic fibrosis clinics in four midlands centres (Birmingham, Nottingham, Peterborough, and Leicester) were reviewed. Subsequently the computer records of 576 patients with cystic fibrosis who were attending clinics in three northern centres (Manchester, Liverpool, and Leeds) were surveyed. All those with possible clinical evidence of liver disease were identified, and their casenotes were then examined. All the patients had undergone repeated abdominal examinations by physicians experienced in treating cystic fibrosis during routine visits to the clinic. From the records the presence of an enlarged liver or spleen (or both) was noted. If a spleen was described as 'palpable' it was considered to be enlarged. The liver was regarded as enlarged when it protruded 3 cm or more below the costal margin and was not apparently pushed down by hyperinflation of the lung. Radiological and ultrasound findings were not considered.

For the 524 patients in the first four centres only, those patients who had raised serum activities of aspartate transaminase, alanine aminotransferase, or γ-glutamyl transpeptidase at any time, but excluding transient increases in the activity of a single enzyme, were noted. These data were incomplete because only 388 (74%) of the group had ever had their liver function tests done.

Evidence of symptomatic biliary disease was sought, but was considered only when symptoms of biliary colic were accompanied by radiographic or ultrasonographic evidence of gall stones. Policies for investigating asymptomatic biliary disease varied among clinics, so the true prevalence of 'silent' biliary disease could not be estimated.

Data about age at diagnosis of liver disease, mode of presentation, history of prolonged neonatal jaundice, family history, presence of oesophageal varices, and liver function tests were gathered. Where available, the age at death and mode of death of patients attending each of the four initial clinics were noted during the 10 years preceding the study.

The prevalence point was 1 June 1988. The χ^2 test was used to assess the significance of differences among groups.

Results

There were similar trends in the prevalence of clinically apparent disease in the data derived from casenotes in the midlands and those derived from databases in the northern survey. The data have therefore been combined to give a study population of 1100 patients with cystic

Table 3 Age at presentation of liver disease (n=39)

Age (years)	*No presenting*
0	2
4	2
5	2
6	3
7	3
8	1
9	5
10	3
11	4
12	2
13	5
14	4
15	1
17	1
19	1

fibrosis. Of these, 46 (4·2%) had clinical liver disease. Eleven (1·0%) had an enlarged liver only, three (0·3%) had an enlarged spleen only, and 32 (2·9%) had enlargement of both liver and spleen. Cutaneous signs of liver disease were recorded in only two.

Oesophageal varices had been sought in 34/46 with clinical disease, and were detected in 11. Of these, all had enlarged spleens, and six had bled at least once. There was no variceal bleeding in patients who did not have enlarged spleens. Six of 46 in the combined clinical group (13·0%) had liver enzyme activities within the reference ranges, and four also had enlarged spleens.

No patient had jaundice or ascites at the time of the study.

The prevalence of abnormal liver enzyme activities in the absence of clinical disease could be estimated only for the midlands group of 524: 50 were identified (9·5%). These represented 12·9% of those who had had liver enzymes measured.

Clinically apparent and radiologically proved biliary disease was rare and restricted to the older age groups. Only six patients out of 1100 (0·55%) were found: one of 183 (0·5%) in the 16–20 age band, three of 107 (2·8%) in the 21–25 band, and two of 38 (4·6%) aged over 25 years.

AGE RELATED PREVALENCE (table 1)

There was a progressive rise in the prevalence of clinically apparent liver disease from 0·3% in the 0–5 age group to a peak of 8·7% among those aged 16–20. Thereafter, instead of the expected progressive rise, there was a fall to only 4·1% among 145 patients over 20 years of age. The same trend was seen when only those with splenomegaly were considered, or when those who had neither an enlarged spleen nor abnormal liver function tests were excluded.

The group with portal hypertension as indicated by an enlarged spleen had a mean age of 15·3 years (range 7–27), and those with oesophageal varices had a mean age of 17·3 years (range 9–27).

Biochemical abnormalities without clinical signs were more prevalent than overt disease (table 2), and showed a similar although less pronounced peak, rising to 16·0% in the 16–20 age group, and falling to 11·5% over 20.

SEX RELATED PREVALENCE

Significantly more male patients were affected by clinical disease, both in the midlands and in the combined populations; 33/605 (5·4%) were affected overall compared with 13/495 (2·6%) of female patients, ($p<0·05$). The difference was seen at all ages over 5 years, and was most pronounced in the 11–15 age group, in which three times as many boys as girls were affected. There were no significant differences between the sexes in the group with biochemical abnormalities only, but prevalence data for this group was incomplete.

AGE AT PRESENTATION OF LIVER DISEASE

Reliable information about the age at which liver disease first became clinically apparent was available for 39 of the 46 with clinical disease. (table 3). The mean age at presentation was 9·8 years (median 10·5).

MODE OF PRESENTATION OF LIVER DISEASE

Of the 46 with clinical disease, it presented in 43 as an incidental finding on abdominal examination: 11 had enlarged liver only, three had enlarged spleen only, and in 29 both organs were enlarged. Two presented with abnormal liver enzyme activities and later progressed to overt disease; one presented with biliary pain. None of the patients presented with prolonged neonatal jaundice. Two presented with hepatosplenomegaly before the diagnosis of cystic fibrosis was made.

SIBLINGS

There were no sibling pairs within the total group of 46 patients with clinical liver disease, although nine of the 46 had one or more siblings with cystic fibrosis. Two, however, had siblings who had died and were known to have had liver disease. At least two had siblings with abnormal liver enzyme activities.

Table 1 Prevalence of clinical liver disease in 5 year age bands. Numbers are expressed as total number (% of number for age)

	Age (years)					*Total*
	0–5	*6–10*	*11–15*	*16–20*	*≥21*	
No of patients with cystic fibrosis	318	258	196	183	145	1100
No (%) with clinical liver disease	1 (0·3)	9 (3·5)	14 (7·1)	16 (8·7)	6 (4·1)	46 (4·2)
No (%) with enlarged spleen	0	6 (2·3)	11 (5·6)	14 (7·6)	4 (2·8)	35 (3·2)
No (%) with either enlarged spleen or abnormal liver function tests	1 (0·3)	7 (2·7)	12 (6·1)	16 (8·7)	6 (4·1)	42 (3·8)

Table 2 Prevalence of biochemical liver disease without clinical signs in midlands centres; 136 (26%) of the total had not had liver function tests carried out. Numbers are expressed as total number (% of number for age)

	Age (years)					*Total*
	0–5	*6–10*	*11–15*	*16–20*	*≥21*	
No of patients with cystic fibrosis	177	125	89	81	52	524
No (%) with biochemical liver disease	10 (5·6)	10 (8·0)	11 (12·4)	13 (16·0)	6 (11·5)	50 (9·5)

CAUSE OF DEATH

The causes of death among those attending the midlands clinics over the past 10 years were reliably ascertained in 80%. For the others records were unavailable, or death had occurred at home and the precise mode had not been recorded. There were 77 deaths during this period (31 male, 46 female), and their mean age was 13·9 years. Only two patients died from acute variceal haemorrhage, and only four from acute liver failure. The mean age at death of these six (three male, three female) was 10·8 years. The remainder died primarily from respiratory causes, but at least six of these had some degree of liver disease.

Discussion

There have been no previous systematic attempts to assess the clinical prevalence of liver disease among patients with cystic fibrosis across the entire age range in a substantial population. Feigelson *et al*, using a variety of criteria, found evidence of cirrhosis in nine of 50 patients with cystic fibrosis between 1 and 20 years old.[16] Stern *et al* described 15 cases with symptomatic liver disease in a population of 693 (2·2%).[14] Schwarz *et al* reported nine cases of overt liver disease among 204 patients all less than 13 years old (4·4%).[17] More recently, Nagel *et al* reported either biochemical or overt liver disease in 57 of 233 patients over 15 years old (24·5%).[18]

Necropsy studies have shown overall rates of abnormal histological appeareances of the liver of 12%,[19] 22%,[5] and 29·5%.[11] The latter series (n=146) suggested an increasing prevalence with age from 10·8% at less than 3 months to 26·8% at over 1 year. Vawter and Schwachman found focal biliary changes in 21 of 29 patients who died after the age of 24 years (72%).[12] Necropsy data may not reflect the true age related prevalence as the presence of liver disease may have contributed to death. None of the published necropsy studies relate the histopathological findings to clinical condition, or to radiological or biochemical abnormalities.

Varying estimates of the prevalence of abnormalities shown on ultrasound scanning have also been reported. Willi *et al* performed scans in 24 unselected patients and found abnormalities in 22 (92%), of whom 10 had specific liver abnormalities.[20] Graham *et al* (in an adult series) found hepatomegaly in 23 of 35 (66%) and abnormal echogenicity in 11 of 35 (31%),[21] and Wilson-Sharp *et al* found hepatic abnormalities in 23% of children.[22]

Data on the results of examination of liver biopsy specimens in patients with cystic fibrosis are scarce, although Dietzsch *et al* found histological evidence of liver disease in 15 of 84 children who underwent needle biopsy (18%).[15] Not all those whose biopsy specimens were abnormal had either clinical or biochemical evidence of liver disease. Trying to identify subclinical liver disease by biopsy is impossible to justify in the absence of any treatment, except in assessment for transplantation.

Thus the assumption of a rising prevalence of liver disease with age in cystic fibrosis is based mainly on necropsy series.[23] In the present study the prevalence of clinically overt disease in 1100 patients with cystic fibrosis was 4·4%, similar to some quoted estimates.[10 23] This is likely to be an underestimate of the true prevalence of focal biliary cirrhosis, as the histopathological changes may precede enlargement of the liver or the development of portal hypertension.

The presence of an enlarged liver in isolation, with no other evidence of liver disease, should be interpreted with caution because this may be the result of depression of a normal liver below the costal margin by hyperinflated lungs, rather than true enlargement. Measuring the liver span by percussion is difficult in patients with cystic fibrosis because the chest is frequently hyperresonant throughout. In our series, however, only four patients had isolated liver enlargement with neither splenomegaly nor abnormal liver function tests, and when these were excluded the same trends in age and sex prevalence were seen.

Liver disease was relatively uncommon before the age of 10 years. Some of the younger patients may have had hepatic steatosis related to poor nutrition rather than cirrhosis.[24] Thereafter, instead of the expected progressive rise into adult life, there was a peak during adolescence followed by a fall in prevalence over the age of 20 years.

There are two possible explanations for this observation. Firstly, it may be an unexplained cohort effect, and further longitudinal studies would show whether the prevalence peak shifts into adult life. Alternatively, because liver disease in cystic fibrosis is irreversible, this trend can be explained by an increase in mortality in the teenage years among those with liver disease. Our review of mortality records for the preceding 10 years showed that only 7·8% of deaths could be attributed directly to liver disease, either hepatocellular failure or portal hypertension. It may therefore be that the presence of liver disease increases the likelihood of premature respiratory death in teenage patients with cystic fibrosis. The rarity of hepatocellular failure as a cause of death may be explained by the histopathology of focal biliary cirrhosis, in which the hepatic parenchyma is left largely intact.[3 4]

The sex distribution of overt disease showed an unexpected preponderance of male patients. No other manifestation of cystic fibrosis shows such a sex difference. It cannot be attributed to the action of sex hormones, as the onset was usually prepubertal. Recently, Becker *et al* showed that female patients with cystic fibrosis had significantly more cholesterol saturation of bile than male patients, but this difference was seen only after puberty. There is reported to be a higher mortality from cystic fibrosis among female compared with male patients in the United Kingdom as a whole,[2] and it is possible that increased mortality among girls with liver disease explains our findings.

Although these data are derived from patients attending specialist cystic fibrosis clinics, and may thus be somewhat selected, they include most of the patients with cystic fibrosis living in the areas served by the clinics. No patients were referred specifically because of liver disease. There is no reason to suppose that the observed trends should be any different for patients who were not attending the clinics.

The findings in the 'biochemical' group, derived from the smaller midlands population only, should be interpreted with caution as there was no consistent policy of monitoring liver enzyme activities among the clinics. Some patients had never had liver function tests done, and in others, increased activities may have been the result of causes other than developing cirrhosis. Liver function tests were carried out more often in older patients. Despite the incomplete data the same age prevalence trend was seen as in patients with overt disease.

Like other authors, we found an inconsistent relationship between hepatosplenomegaly and abnormal liver enzyme activities. Kattwinkel *et al* in their study of liver enzyme activities in patients with cystic fibrosis compared with age matched controls found that 15/40 (38%) had raised alkaline phosphatase liver isoenzyme activity.[13] They also found raised γ-glutamyl transpeptidase, aspartate aminotransferase, and alanine aminotransferase activities in a similar proportion of patients, but only six of 11 patients with palpable livers had abnormal tests, while 11/38 whose livers were not palpable had abnormal tests. We therefore doubt the value of routine monitoring of liver enzyme activities in patients with cystic fibrosis. No evidence has been published to establish the value of other biochemical or haematological tests, including dynamic tests of liver function such as caffeine clearance, in predicting the later occurrence of overt disease.

Subclinical biliary disease is thought to be common among adults with cystic fibrosis. In one study 17 of 23 adults with abnormal liver enzyme activities had abnormalities on biliary imaging,[18] and this was suggested to be the primary hepatobiliary lesion in cystic fibrosis.[7] We found symptoms of biliary disease to be rare.

The mode of presentation of liver disease was by routine abdominal examination in most patients, and in only two of 46 of the clinical group (4%) was the development of overt disease predicted by abnormal liver function tests. We found no strong evidence of familial concordance as reported by Schuster *et al.*[26]

As expected, 20% of those with overt disease had oesophageal varices although, because not all patients had been recently investigated, the true incidence may have been higher. Enlargement of the spleen seems to predict those at risk from haemorrhage.

In conclusion, these data suggest that the prevalence of liver disease in cystic fibrosis peaks during adolescence, affects male more than female patients, and seems to be associated with earlier death. Those with liver disease may thus form an identifiable group with a worse prognosis who warrant more aggressive treatment. Poor nutritional state associated with liver disease may contribute to the shorter life span, but data are lacking. Clinical signs are probably a late sign of liver disease, but results of liver function tests are unreliable. The cause, future changes in prevalence, and the prognosis of liver disease in cystic fibrosis demand further study.

We thank the Cystic Fibrosis Research Trust for funding this study. We also thank colleagues in the cystic fibrosis clinics in Leicester, Nottingham, Birmingham, Peterborough, Leeds, Liverpool, and Manchester for allowing us to search their records, and in particular Dr EJ Hiller, Dr P Weller, and Dr J Kuzemko for help in setting up the study.

1 Andersen DH. Cystic fibrosis of the pancreas. *Am J Dis Child* 1938;**56**:344–99.
2 Britton JR. Effects of social class, sex, and region of residence on age at death from cystic fibrosis. *BMJ* 1989;**298**:483–7.
3 Bodian M. *Fibrocystic disease of the pancreas. A congenital disorder of mucus production-mucosis*. London: William Heinemann, 1952:106–10.
4 Webster R, Williams H. Hepatic cirrhosis associated with fibrocystic disease of the pancreas. *Arch Dis Child* 1953;**28**:343–50.
5 di Sant'Agnese PA, Blanc WA. A distinctive type of biliary cirrhosis of the liver associated with cystic fibrosis of the pancreas. *Pediatrics* 1956;**18**:387–409.
6 Mieli-Vergani G, Psacharopoulos HT, Nicholson AM, *et al.* Immune responses to liver membrane antigens in patients with cystic fibrosis and liver disease. *Arch Dis Child* 1980;**55**:696–701.
7 Gaskin KJ, Waters DLM, Howman-Giles R, *et al.* Liver disease and common bile-duct stenosis in cystic fibrosis. *N Engl J Med* 1988;**318**:340–6.
8 Maurage C, Lenaerts C, Weber A, Brochu P, Yousef I, Roy CC. Meconium ileus and its equivalent as a risk factor for the development of cirrhosis: an autopsy study in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1989;**9**:17–20.
9 Isenberg JN. Cystic fibrosis: its influence on the liver, biliary tree, and bile salt metabolism. *Semin Liver Dis* 1982;**2**:302–13.
10 Park RW, Grand RJ. Gastrointestinal manifestations of cystic fibrosis: a review. *Gastroenterology* 1981;**81**:1143–61.
11 Oppenheimer EH, Esterly JR. Hepatic changes in young infants with cystic fibrosis: possible relation to focal biliary cirrhosis. *J Pediatr* 1975;**86**:683–9.
12 Vawter GF, Schwachman H. Cystic fibrosis in adults: an autopsy study. *Pathol Annu* 1979;**14**:357–82.
13 Kattwinkel J, Taussig LM, Statland BE, Verter JI. The effects of age on alkaline phosphatase and other serologic liver function tests in normal subjects and patients with cystic fibrosis. *J Pediatr* 1973;**82**:234–42.
14 Stern RC, Stevens DP, Boat TF, Doershuk CF, Izant RJ, Matthews LW. Symptomatic hepatic disease in cystic fibrosis: incidence, course, and outcome of portal systemic shunting. *Gastroenterology* 1976;**70**:645–9.
15 Dietzsch HJ, Gottschalk B, Hinkel GK, Roschlav G. The value of bioptic follow-up examinations for controlling the course of liver involvement in cystic fibrosis. In: Sturgess JM, ed. *Perspectives in cystic fibrosis*. Toronto: Canadian Cystic Fibrosis Foundation, 1980:220–5.
16 Feigelson J, Pecau Y, Cathelineau L, Navarro J. Additional data on hepatic function tests in cystic fibrosis. *Acta Paediatr Scand* 1975;**64**:337–44.
17 Schwarz HP, Kraemer R, Thurnheer U, Rossi E. Liver involvement in cystic fibrosis. *Helv Paediatr Acta* 1978;**33**:351–64.
18 Nagel RA, Westaby D, Javaid A, *et al.* Liver disease and bile duct abnormalities in adults with cystic fibrosis. *Lancet* 1989;ii:1422–5.
19 Luftner J, Scheibner K, Woeckel W. Zur hepatischen Manifestation der Mukoviszidose. *Zentralbl Allg Pathol* 1977;**121**:195–200.
20 Willi UV, Reddish JM, Teele RL. Cystic fibrosis: its characteristic appearance on abdominal ultrasonography. *AJR* 1980;**134**:1005–10.
21 Graham N, Manhire AR, Stead RJ, Lees WR, Hodson ME, Batten JC. Cystic fibrosis: ultrasonographic findings in the pancreas and hepatobiliary system correlated with clinical data and pathology. *Clin Radiol* 1985;**36**:199–203.
22 Wilson-Sharp RC, Irving HC, Brown RC, Chalmers DM, Littlewood JM. Ultrasonography of the pancreas, liver, and biliary system in cystic fibrosis. *Arch Dis Child* 1984;**59**:923–6.
23 Roy CC, Weber AM, Morin CL, *et al.* Hepatobiliary disease in cystic fibrosis: a survey of current issues and concepts. *J Pediatr Gastroenterol Nutr* 1982;**1**:469–78.
24 Thaler H. Relation of steatosis to cirrhosis. *Clinics in Gastroenterology* 1975;**48**:273–80.
25 Becker M, Staab D, Leiss O, Von Bermann K. Biliary lipid composition in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1989;**8**:308–12.
26 Schuster SR, Schwachman H, Toyama WM, Rubino A, Taik-Khaw K. The management of portal hypertension in cystic fibrosis. *J Pediatr Surg* 1977;**12**:201–6.

Archives of Disease in Childhood 1991; **66:** 702–705

Imaging in influenza A encephalitis

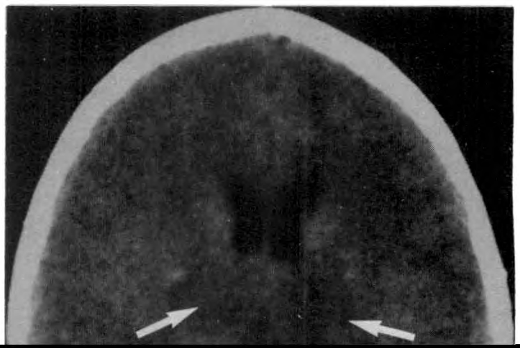
S M Protheroe, D H Mellor

Abstract

Two cases of influenza A encephalitis seen during an outbreak of influenza types A/England/427/88 (H3N2) and A/Taiwan/1/86 (H1N1) in December 1989 are described. In both children the encephalitis developed within three days of the respiratory symptoms and both became comatose within 48 hours. Virological studies showed that the patients had had a recent influenza A infection. Symmetrical localised hypodense lesions within the thalami and pons were demonstrated in both cases on computed tomography of the brain and striking findings in the pons in one case on magnetic resonance imaging. Influenza A encephalitis is not easy to recognise clinically and serological confirmation can only be made after 10 days. Imaging may provide evidence in the acute stage to support a diagnosis of influenza encephalitis during

acids were also normal. Electroencephalography showed generalised slow wave activity.

Computed tomography of the brain on the second day showed low attenuation changes in the thalami bilaterally (fig 1). There was some brainstem swelling with low attenuation change in the pons (fig 2). Both putamina and globus



[redacted]

pallidi showed small foci of high attenuation possibly representing haemorrhage.

On the third day his condition deteriorated with decorticate posturing, early papilloedema, and a sixth nerve palsy on the right. Dexamethasone was started, he was ventilated, and an intracranial pressure monitoring device was inserted. He was treated with acyclovir and thiamine, although the features were not typical or herpes simplex encephalitis or Leigh's disease.

He was extubated after four days but remained in a somnolent state. By day 10 he had begun to improve, although he showed choreoathetoid movements of his trunk and limbs on purposeful movement. Complement fixation titre for influenza A virus was less than 16 on admission, but increased to +256 on the 15th day, indicating recent influenzal infection. Serological tests failed to demonstrate any other virus antibody response and we were not able to find any other cause for coma or encephalopathy.

He was discharged on day 28, walking with an aid and speaking in sentences. Follow up three months later showed he had made a full neurological and intellectual recovery apart from a persisting right lateral rectus palsy.

CASE 2

An 11 year old girl was admitted having been found semicomatose by her parents. For the previous three days she had been febrile with headache, cough, and malaise. Two family members also had influenza like symptoms. She had had an acute encephalitis at age 3, from which she had recovered, but had been left with residual behavioural problems, left divergent squint, precocious puberty, and mild optic atrophy. This episode had also followed an upper respiratory tract infection and influenza A was isolated from a throat swab. Computed tomography of the brain at that time had shown linear hypodensities in the external capsule region on both sides.

On this occasion she was drowsy but able to respond to commands on admission. Pale optic discs were noted as before. She was pyrexial and had brisk tendon reflexes with extensor plantar responses. The cerebrospinal fluid showed a raised protein concentration (1·2 g/l) with no white cells, 36 red cells/mm^3, and normal glucose. Serum electrolytes, ammonia, hepatic function tests, copper, caeruloplasmin, lactate, and a full blood count were within normal limits, as were urine amino acids and organic acids. Trichrome staining of a muscle biopsy specimen showed no 'ragged red muscle fibres'.

She became unrousable by the second day and was unresponsive to pain with loss of the gag reflex. Central respiratory irregularities, namely hyperventilation and Cheyne-Stokes respiration became apparent, and she was intubated and ventilated. She was treated with acyclovir and dexamethasone.

Computed tomography of the brain showed symmetrical well defined areas of low attenuation in both thalami extending to involve the capsular fibres. Further diffuse low attenuation changes were seen within the pons and midbrain. Some swelling of the brainstem was seen. Low attenuation changes considered longstanding and a result of her previous encephalitis were noted in the external capsules. Magnetic resonance imaging inversion recovery sequences of the brain showed low signal changes in the thalami and pons (fig 3). Axial T2 weighted images showed ring like areas of high signal intensity with central low signal in the pons (fig 4). Complement fixation titres for influenza A virus were less than 16 on admission but increased to +256 by day 15.

By day 17 of her illness it was possible to take her off the ventilator and extubate her. She opened her eyes to sensory stimuli but did not recognise her parents. Spasticity affected all four limbs; she was unable to swallow and required tube feeding. She remained in this 'sleeping beauty, akinetic mute' state for three months without much change. Progress was very slow and five months after the onset of her illness she was still immobile with expressionless facies and paucity of movement. She could sit in a chair with support and recognise her

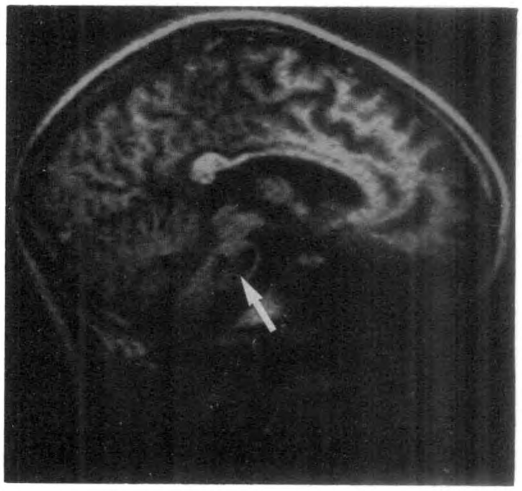


Figure 3 Saggital inversion recovery magnetic resonance imaging brain scan in case 2 showing low signal changes in the pons (arrowed).

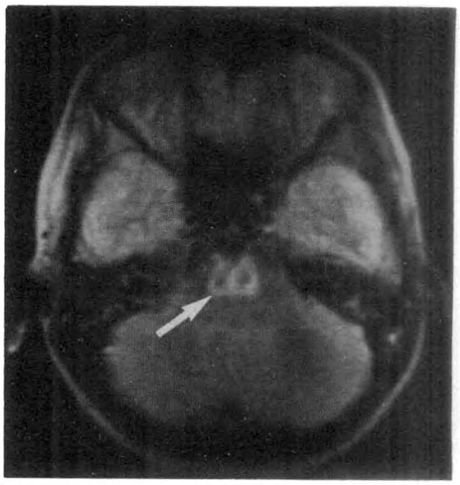


Figure 4 Axial T2 weighted magnetic resonance imaging brain scan in case 2 showing ring like areas of high signal in the pons (arrowed).

parents. Speech had not returned but she could use a simple communication board and understand simple sentences.

Discussion

These two children were considered to have influenza A encephalitis on the basis of the prodromal illness, clinical course, and virology studies. Clinically they resemble the six cases described by Delorme and Middleton, who developed fever, reduced consciousness, and neurological signs after influenzal symptoms.[4] Analyses of the cerebrospinal fluid were normal in these six cases apart from a slight increase in protein in one patient, but computed tomography was not done.

True encephalitis is comparatively rare after influenza A but benign confusional states and minor neurological signs (for example, ocular muscle palsies) are observed more often.[5] Parainfectious processes such as transverse myelitis and Reye's syndrome are also observed,[4–10] although virus isolation from the brain or cerebrospinal fluid is infrequent.[11 12] Neurological symptoms and signs may appear several weeks after the infection making it difficult to establish an aetiological link in some cases.

The finding of focal low attenuation lesions in the frontotemporal regions on computed tomography can be helpful in the diagnosis of herpes simplex encephalitis.[13 14] Computed tomography is usually diagnostically unrewarding in other forms of encephalitis. However, our findings suggest that there may be a typical appearance on computed tomography in influenza encephalitis, and this is in keeping with two reports from Japan describing similar localised hypodense lesions.[2 3] Recognition of these tomographic abnormalities in patients with possible influenzal encephalitis may aid diagnosis while viral titres are awaited.

The findings on magnetic resonance imaging in brainstem encephalitis include pontine enlargement and increased signal lesions in the pons.[15 16] Magnetic resonance imaging is superior to computed tomography for detecting brainstem encephalitis, as seen in our second case where obvious pontine abnormalities were shown on magnetic resonance imaging but not well seen on computed tomography. A similar discrepancy between magnetic resonance imaging and tomography findings in brainstem encephalitis has been previously reported where discrete abnormal areas were seen in the pons, midbrain, and thalamus on magnetic resonance imaging but the computed tomogram had revealed only a low density area in the pons.[17]

It has been observed that a normal computed tomogram on follow up correlates with full clinical recovery in viral encephalitis in general.[18 19] This is also seen in the previously reported case of influenza A encephalitis where the initial abnormal hypodense areas in the midbrain, basal ganglia, and cerebral white matter had disappeared on follow up computed tomography and the patient made a good recovery.[3]

The cause of these lesions is unknown. It has been postulated that hypodense areas on computed tomography in encephalitis reflect the sequelae of ischaemia induced by compression of end arteries by brain oedema or may be due to localised areas of inflammation. It is known that the virus can have a direct cytopathic effect on vulnerable sites.[2 7]

Our second case experienced two episodes of acute encephalitis when infected with influenza A, which could not be explained by any other identifiable cause. On both occasions there was virological evidence of recent influenza infection. The original episode was associated with bilateral hypodense areas in the external capsule regions on computed tomography, with low attenuation lesions in both thalami, pons, and midbrain on the second scan.

Localised hypodense lesions in the basal ganglia have also been described on computed tomography in encephalitis after infections with ECHO, mumps, measles, and Coxsackie viruses.[18 20 21] Other causes of low density areas in the basal ganglia and thalamus have been described in disorders such as Leigh's encephalopathy, Wilson's disease, and mitochondrial cytopathies as well as carbon monoxide poisoning and anoxia.[22] Wilson's disease, Leigh's encephalopathy, and mitochondrial cytopathies seem unlikely in view of the normal copper studies and lactate concentrations in both cases and the normal muscle biopsy specimen in case 2.

Circumstantial evidence has implicated the influenza virus as the cause of the encephalitis lethargica epidemic of the 1920s.[23] Similar isolated cases have been described from year to year often at the time of influenza epidemics.[24–29] von Economo first described the illness, postulated a viral aetiology, and reported foci of inflammation in the grey matter of the midbrain and basal ganglia.[30] The manifestations of encephalitis lethargica were variable but a number of clinical features have been proposed as major criteria to support the diagnosis.[31] Our first case showed signs of basal ganglia involvement with choreoathetoid movements, ophthalmoplegia, and somnolence. Our second case exhibited akinetic mutism, central respiratory irregularities, and somnolence. Combined with the acute encephalitic illness, our cases fulfil the criteria to support the diagnosis of encephalitis lethargica. We are aware that unexpected neurological sequelae such as parkinsonism with oculogyric crises can appear after apparent recovery as long as four years later.

1 PHLS Communicable Disease Surveillance Centre. *Communicable disease report. CDR 89/44*. London: CDSC, 1989; 3rd November: 3–4.

2 Hattori H, Kawamori J, Takao T, *et al*. Computed tomography in postinfluenzal encephalitis. *Brain Dev* 1983;5: 564–7.

3 Okuno T, Takao T, Ito M, Mikawa H, Nakano Y. Contrast enhanced hypodense areas in a case of acute disseminated encephalitis following influenza A virus. *Comput Radiol* 1982;6:215–7.

4 Delorme L, Middleton PJ. Influenza A virus associated with acute encephalopathy. *Am J Dis Child* 1979;13:822–4.

5 Sulkava R, Rissanen A, Pyhala R. Post-influenza encephalitis during the influenza A outbreak in 1979/80. *J Neurol Neurosurg Psychiatry* 1981;**44**:161–3.

6 Wells CEC. Neurological complications of so-called 'influenza' winter study in S E Wales. *BMJ* 1971;i:369–73.

7 Booss J, Esiri M. Epidemic encephalitis I. *Viral encephalitis. Pathology, diagnosis and treatment*. Oxford: Blackwell Scientific Publications, 1986:141.

8 Flewett TH. Influenzal encephalopathy and post-influenzal encephalitis. *Lancet* 1958;ii:11–5.

9 Dubowitz V. Influenzal encephalitis. *Lancet* 1958;i:140.

10 Horner FA. Neurological disorders after Asian influenza. *N Engl J Med* 1958;**258**:983–5.
11 Anonymous. News and Notes. Epidemiology. Laboratory Reports. *BMJ* 1970;**i**:311.
12 Frankova V, Jirasek A, Tumova B. Type A influenza virus isolations from different organs in human lethargica cases. *Arch Virol* 1977;**53**:265–8.
13 Thompson JLG. The computed axial tomography in acute herpes simplex encephalitis. *Br J Radiol* 1976;**49**:86–7.
14 Davis JM, Davis KR, Leinman GM, Kirchner HS, Taveras JM. Computed tomography of herpes simplex encephalitis with clinicopathological correlation. *Radiology* 1978;**129**: 409–17.
15 Davidson HD, Steiner RE. Magnetic resonance imaging in infections of the central nervous system *AJNR* 1985;**6**: 499–504.
16 Furman JM, Brownstone PH, Baloh RN. A typical brainstem encephalitis magnetic resonance imaging and oculographic features. *Neurology* 1985;**35**:438.
17 Hosoda K, Tamaki N, Masumoa M, Matsumoto S. Magnetic resonance images of brainstem encephalitis. *J Neurosurg* 1987;**66**:283–5.
18 Charney R, Orecchio EJ, Simmerman RA, Berman RH. Computerised tomography in infantile encephalitis. *Am J Dis Child* 1979;**133**:803–5.
19 Bittner T, Dorndorf W. Prognostic value of computerised tomography and cerebrospinal fluid analysis in viral encephalitis. *J Neuroimmunol* 1988;**20**:16.
20 Goutieres F, Aicardi J. Acute neurological dysfunction associated with destructive lesion of the basal ganglia in children. *Ann Neurol* 1982;**12**:328–32.
21 Ochi J, Okuno T, Uenoyama Y, Narita H, Mikawa H. Symmetrical low density areas in bilateral thalami in an infant with measles encephalitis. *Comput Radiol* 1986;**10**: 137–9.
22 Aicardi J, Gordon N, Hagberg B. Holes in the brain. *Dev Med Child Neurol* 1985;**25**:249–60.
23 Maurizi CP. Influenza caused epidemic encephalitis (encephalitis lethargica). The circumstantial evidence and challenge to the naysayers. *Med Hypotheses* 1989;**28**:18.
24 Leigh AD. Infections of the nervous system occurring during an epidemic of influenza B. *BMJ* 1946;**ii**:936.
25 Espir MLE, Spalding JMK. Three recent cases of encephalitis lethargica. *BMJ* 1956;**i**:1141–4.
26 Hunter R, Jones M. Acute lethargic type encephalitis. *Lancet* 1966;**ii**:1023–4.
27 Anonymous. Encephalitis of lethargica type in a mental hospital [Editorial]. *Lancet* 1966;**ii**:1014–5.
28 Greenough A, Davis JA. Encephalitis lethargica. Mystery of the past or undiagnosed disease of the past? *Lancet* 1983;**i**: 922–3.
29 Anonymous. Encephalitis lethargica [Editorial]. *Lancet* 1981; **ii**:1396.
30 von Economo C. *Encephalitis lethargica: its sequelae and treatment.* Translated by KO Newman. London: Oxford University Press, 1931.
31 Howard RS, Lees AJ. Encephalitis lethargica. A report of four recent cases. *Brain* 1987;**110**:19–33.

Addendum

Since this paper was accepted for publication case 1 was readmitted to hospital after a seizure at home. Vomiting and a further seizure occurred after admission. He was drowsy and febrile but there was no neck stiffness and no focal neurological findings. Blood urea, electrolytes, glucose, prothrombin time, liver function tests, haemoglobin, and platelets were normal. Total peripheral white cell count was low at $2{\cdot}2\times10^9$/l.

He was given an intravenous loading dose of phenytoin. Computed tomography showed no changes. The cerebrospinal fluid was sampled and contained one lymphocyte/mm^3, a normal glucose, but a raised protein concentration of 1·6 g/l, and a pressure of 35 cm H_2O. Further short seizures occurred and then a respiratory arrest requiring resuscitation and mechanical ventilation. Despite passive hyperventilation and mannitol his pupils remained fixed and dilated. Brainstem function tests showed no activity and ventilatory support was withdrawn after a period of 12 hours. Permission for postmortem examination was not given. Subsequently the results of viral antibody titres sent on admission became available. All were negative including influenza A and B.

COMMENT

The previous encephalitis had occurred in association with a serologically proved influenza infection. This fatal illness a year later raises the possibility that the original illness could have been some kind of metabolic encephalopathy precipitated by the influenza, although detailed metabolic investigations were negative.

Archives of Disease in Childhood 1991; **66**: 706–709

Occurrence, clinical manifestations, and prognosis of Guillain-Barré syndrome

H Rantala, M Uhari, M Niemelä

Abstract

In order to obtain more information on the incidence of Guillain-Barré syndrome and recent developments in its prognosis, we analysed the severity and prognosis of Guillain-Barré syndrome in children diagnosed and treated during the years 1980–6 throughout Finland. The criteria for Guillain-Barré syndrome were fulfilled in 14 boys and 13 girls. The mean annual number of cases of Guillain-Barré syndrome was thus 3·9, giving a mean annual incidence of 0·38/100 000 of population under 15 years of age (95% confidence intervals 0·25 to 0·56/100 000). The incidence of Guillain-Barré syndrome causing permanent neurological defects in children under 15 years of age was 1·4/10 million annually (95% confidence intervals 0·035 to 7·8/10 million). Our figures appeared to be one fourth to a half of that reported earlier in children and even lower than those in adults. Although there were no deaths among our patients, mortality from Guillain-Barré syndrome seems to have remained similar for the last 20 years despite current awareness of the possibility of cardiac arrest and respiratory failure.

The overall annual incidence of the Guillain-Barré syndrome has been estimated to be 1·7/100 000 persons,[1] but no separate incidence figures are available for children. Similarly our knowledge of the impact of Guillain-Barré syndrome at the population level is incomplete. In general, reports concerning Guillain-Barré syndrome in children are based on patients treated in one referral hospital,[1–8] which may cause bias in assessments of the severity of Guillain-Barré syndrome, as the worst cases are most likely to be reported. On the other hand, its severity and prognosis in childhood have been evaluated in surveys involving patients treated mainly during 1960–70.[1–7] In these series mortality varied up to a maximum of 9%,[6] most of the deaths being caused by cardiac arrest or respiratory failure.[8] It may be that the awareness of these events and the better possibilities for treating such patients have improved the prognosis for Guillain-Barré syndrome during the last 10 years.

In order to obtain more information about the incidence of Guillain-Barré syndrome and recent developments in its prognosis, we analysed its severity and prognosis in children, reviewing the literature and the records of patients diagnosed and treated during the years 1980–6 over the whole of Finland.

Department of Paediatrics, University of Oulu, SF-90220 Oulu, Finland
H Rantala
M Uhari
M Niemelä

Correspondence and requests for reprints to:
Dr Uhari.

Accepted 1 February 1991

Patients and methods

SOURCES OF DATA

The Finnish National Board of Health keeps a central database on the diagnosis, sex, and age of the patients discharged from all the hospitals in the country. Patients discharged during the period from 1 January 1980 to 31 December 1986 from paediatric wards with a diagnosis of any kind of polyneuropathy were listed and their case histories reviewed by us. The mean population at risk in Finland during 1980–6 was 1·02 million.

CRITERIA FOR GUILLAIN-BARRÉ SYNDROME

The findings listed by the Guillain-Barré syndrome study group were used as criteria (table 1).[9] The case histories of 83 children were reviewed by a paediatric neurologist (HR) and 14 boys and 13 girls were found to fulfil the criteria.

STATISTICAL METHODS

The occurrence of cases of Guillain-Barré syndrome was assumed to follow an even distribution in time and place. Confidence intervals were calculated based on a Poisson distribution.

Results

The mean annual number of cases of Guillain-Barré syndrome was 3·9, giving a mean annual incidence of 0·38/100 000 of population under 15 years of age (95% confidence intervals 0·25 to 0·56/100 000). The incidence of Guillain-Barré syndrome causing permanent neurological defects in children under 15 years of age was 1·4/10 million annually (95% confidence intervals 0·035 to 7·8/10 million). The patients were evenly distributed in terms of age, which varied between 0·4 and 14·3 years. A preceding infection was verified in 23 patients with respiratory symptoms occurring most frequently (n=18). A vaccination before the symptoms was recorded in 11 patients.

The disease began from the lower extremities in 25 patients, one had paresis of the urinary bladder as the first sign of the disease, and one had paraesthesia (table 1). Nine had facial palsy, three had paresis of the abducens nerve, one had a bilateral hypoglossus paresis, and two had bulbar paresis. Twenty children had pain in the back or in the lower extremities two to 14 days before the onset of the neurological defects. Four children had meningism. An increase in blood pressure requiring medical treatment was found in one patient.

Table 1 Diagnostic criteria for the Guillain-Barré syndrome as laid down by the Guillain-Barré syndrome study group,[9] and numbers of patients fulfilling the criteria in the present series

Criteria	*No of patients*
Features required for diagnosis:	
Progressive motor weakness in more than one limb	27
Areflexia or appreciable hyporeflexia	27
Cerebrospinal fluid cell counts of no more than $50/mm^3$ monocytes or $2/mm^3$ polymorphonuclear leukocytes	26*
Features strongly supportive of the diagnosis:	
Progression over some days to a few weeks	27
Cranial nerve involvement	13
Onset of recovery two to four weeks after half in progression	27
Raised cerebrospinal fluid protein after one week of symptoms	26*
Abnormal electrodiagnostics with slowed conduction or prolonged F waves	20

*Lumbar puncture was not performed on one patient because of a suspicion of increased intracranial pressure.

A lumbar puncture was performed in all cases except one, where it was avoided because of a suspicion of increased intracranial pressure. Protein concentration in the cerebrospinal fluid was increased in all the patients (mean (SD) 1177 (774) mg/l). None had pleocytosis.

Five children needed assisted ventilation, all of whom received corticosteroids, and a plasmapheresis was performed on three of them. No one else received corticosteroids or plasmapheresis. The symptoms worsened over one to 33 days (mean 8·5 days), but none of the patients died. The duration of hospitalisation varied from four to 70 days (mean 34·1 days).

Eighteen children required physiotherapy for a period of three weeks to 22 months (mean 155 days) after discharge from hospital. All the children became symptomless in 22 days to 22 months (mean 158 days), except for one girl who still has a severe sensory neuropathy 5·5 years after the acute phase.

Discussion

The annual incidence of Guillain-Barré syndrome in children under 15 years of age 0·38/100 000 is very low compared with that in adults. Kennedy *et al* found a lower incidence of Guillain-Barré syndrome among patients less than 40 years of age than in older ones, the incidence rates being 1·1 and 3·3/100 000 of population, respectively.[1] They did not give any separate incidence figures for children, however. Our figures are one fourth or a half of those reported in Western Australia, which were 1·13/100 000 in children of 0–9 years of age and of 0·62/100 000 in patients of 10–19 years of age.[10] The figures are not fully comparable, however, as the numbers of children under 15 years of age are not available from their data.[10]

Our study covered the whole population for seven years, during which there was a cluster of Guillain-Barré syndrome temporally associated with an oral polio vaccine campaign.[11] Thus our figures, if anything, are somewhat higher than the real incidence. The cases were collected starting with a loose initial diagnosis to ensure that all cases were found. The heads of the paediatric wards in the country were aware that we were collecting cases of Guillain-Barré syndrome during 1980 to 1986 and this improved our coverage. Thus it is very unlikely that any significant number of cases were left unrecorded. Sometimes Guillain-Barré syndrome is difficult to diagnose, however, and those with a totally wrong diagnosis or a mild clinical symptomatology with myalgia and temporal muscular weakness could have been left out of our survey.

Although the acute symptoms were severe in most cases, the outcome was good. The symptoms of Guillain-Barré syndrome did not differ significantly from those in earlier reports,[1–8] but the great number of children with severe muscle pain was striking and caused differential diagnostic difficulties. There was no mortality, and the incidence of late sequelae was only 1·4/10 million children under 15 years of age. Earlier reports have mentioned mortality due to cardiac arrest or respiratory insufficiency because of either bulbar paresis or paresis of the respiratory muscles.[6 8] Cole and Matthew emphasised the importance of the possibility of aspiration, which may unexpectedly precipitate the need for mechanical ventilation.[8] Oral feeding should be avoided in the presence of bulbar involvement and poor respiratory function. Fluid balance should be ensured by intravenous infusion whenever there is any indication of autonomic disturbances and whenever oral feeding has been denied. Pulmonary collapse or consolidation was not a problem in our patients, which may indicate that the doctors were aware of the dangers of oral feeding in cases of Guillain-Barré syndrome. None of our patients had cardiac involvement, nor were reports found of cardiac arrhythmias treated with a pacemaker. The use of artificial pacing might nevertheless be one important improvement achieved in the treatment of Guillain-Barré syndrome.

The five children with the most severe symptoms in our survey needed assisted ventilation and received corticosteroids, and plasmapheresis was also performed on three of them. All returned to full health without any sequelae. The prognosis cannot be predicted on the basis of the severity of the acute phase.[8] There is no evidence of corticosteroids being effective.[12] In the controlled trials of plasmapheresis in adults it has been found to be either ineffective or to have shortened the duration of severe weakness and assisted ventilation, but no effect has been reported on the mortality.[9 13 14] The experience of plasmapheresis in Guillain-Barré syndrome in children is limited. Khatri *et al* reported good clinical responses in their uncontrolled series of 11 children with Guillain-Barré syndrome.[15] If plasmapheresis is to be used it should be employed in the early phase of the disease and by those who have experience with intensive plasmapheresis in paediatric patients.[15] Recently it has been reported that intravenously administered immune serum globulin may be beneficial in childhood Guillain-Barré syndrome.[16]

No temporal trend in the prognosis was found in the combined data on Guillain-Barré

Table 2 Prognosis for Guillain-Barré syndrome in different studies

Authors	*Time*	*No of patients*	*Selection*	*No (%) of deaths*	*Assisted ventilation*
Markland and Riley[5]	1951–63	19	Hospital	0	—
Paulson[6]	1961–8	46	Hospital	4 (9)	11
Briscoe *et al*[17]	1970–85	24	Hospital	1 (4)	1
Evans[18]	1971–7	18	Hospital	0	2
Hogg *et al*[19]	1972–6	5	Population	1 (20)	1
Kleyweg *et al*[20]	1975–87	18	Hospital	2 (11)	4
Cole and Matthew[8]	1977–84	11	Hospital*	2 (18)	11
Present series	1980–6	27	Population	0	5
Combined		168		10 (5·9)	35

*Only those needing assisted ventilation were included.

syndrome in children (table 2). Although we found no mortality, our survey did not significantly differ from those reported earlier. The frequency of the need for assisted ventilation of 5/27 is a common figure, indicating that our patients represent a typical series of cases of Guillain-Barré syndrome despite being based on a nationwide survey.

Although Guillain-Barré syndrome is a rare disease with a relatively good long term outcome, it causes a long period of hospitalisation and a prolonged need for rehabilitation. The Guillain-Barré syndrome is still a serious and sometimes life threatening condition.

This research was supported financially by the Paulo Foundation, Helsinki, Finland.

1 Kennedy RH, Danielson MA, Mulder DW, Kurland LT. Guillain-Barré syndrome. A 42-year epidemiologic and clinical study. *Mayo Clin Proc* 1978;**53**:93–9.
2 Casamajor L, Alpert GR. Guillain-Barré-Strohl syndrome in children. *Am J Dis Child* 1941;**61**:99–107.
3 Low NL, Schneider J, Carter S. Polyneuritis in children. *Pediatrics* 1958;**22**:972–90.
4 Peterman AF, Daly DD, Dion FR, Keith HM. Infectious neuronitis (Guillain-Barré-Strohl syndrome) in children. *Neurology* 1959;**9**:533–9.
5 Markland LD, Riley HD. The Guillain-Barré syndrome in childhood. *Clin Pediatr (Phila)* 1967;**6**:162–70.
6 Paulson GW. The Landry-Guillain-Barré-Strohl syndrome in childhood. *Dev Med Child Neurol* 1970;**12**:604–7.
7 Rossi LN, Mumenthaler M, Lutschg J, Ludin HP. Guillain-Barré syndrome in children with special reference to the natural history of 38 personal cases. *Neuropaediatrie* 1976;**7**: 42–51
8 Cole GF, Matthew DJ. Prognosis in severe Guillain-Barré syndrome. *Arch Dis Child* 1987;**62**:288–91.
9 The Guillain-Barré Syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. *Neurology* 1985;**35**: 1096–104.
10 Hankey GJ. Guillain-Barré syndrome in Western Australia, 1980–1985. *Med J Austr* 1987;**146**:130–3.
11 Uhari M, Rantala H, Niemelä M. Cluster of childhood Guillain-Barré cases after an oral polio vaccine campaign. *Lancet* 1989;**ii**:440–1.
12 Hughes RAC, Newsom-Davis JM, Perkins GD. Controlled trial of prednisolone in acute polyneuropathy. *Lancet* 1978; **ii**:750–3.
13 Greenwood RJ, Newsom-Davis J, Hughes RAC, *et al.* Controlled trial of plasma exchange in acute inflammatory polyradiculoneuropathy. *Lancet* 1984;**i**:877–9.
14 Osterman PG, Fagius J, Lundemo G, *et al.* Beneficial effects of plasma exchange in acute inflammatory polyradiculoneuropathy. *Lancet* 1984;**ii**:1296–9.
15 Khatri BO, Flamini JR, Baruah JK, Dobyns WB, Konkol RJ. Plasmapheresis with acute inflammatory polyneuropathy. *Pediatric Neurology* 1990;**6**:17–9.
16 Shahar E, Murphy EG, Roifman CM. Benefit of intravenously administered immune serum globulin in patients with Guillain-Barré syndrome. *J Pediatr* 1990;**116**:141–4.
17 Briscoe DM, McMenamin JB, O'Donohoe NV. Prognosis in Guillain-Barré syndrome. *Arch Dis Child* 1987;**62**:733–5.
18 Evans OB. Polyneuropathy in childhood. *Pediatrics* 1979;**64**: 96–105.
19 Hogg JE, Kobrin DE, Schoenberg BS. The Guillain-Barré syndrome epidemiologic and clinical features. *J Chronic Dis* 1979;**32**:227–31.
20 Kleyweg RP, van der Meché FG, Loonen MCB, de Jonge J, Knip B. The natural history of the Guillain-Barré syndrome in 18 children and 50 adults. *J Neurol Neurosurg Psychiatry* 1989;**52**:853–6.

Commentary

Rantala and colleagues report an age specific annual incidence of 0·38/100 000. Similar figures have been reported from Denmark,[1] Norway,[2] and the USA.[3] The last mentioned study reported a linear increase in incidence with increasing age throughout childhood and adult life. These reports, however, can only describe the course of the condition in cases in whom the correct diagnosis is made.

Hospital based reports have emphasised the difficulties of diagnosis, especially in children. Three of the last five personal cases have been referred for the first time after cardiac arrest and still bearing other diagnoses. Of the remaining two, one had been misdiagnosed as encephalitis and the other had prominent pain and cramps, preserved reflexes and reasonable preservation of power at the time when cerebrospinal fluid examination and neurophysiology confirmed the diagnosis.

The classical signs of limb weakness and hyporeflexia may be unimpressive early in the illness. Again, abnormalities of cerebrospinal fluid protein and nerve conduction velocity may not be striking early in the illness. The Guillain-Barré study group listed,[4] in addition to those features tabulated by Rantala *et al*, the following other clinical features strongly supportive of the diagnosis: mild sensory signs or symptoms, autonomic dysfunction, initial absence of fever, and relative symmetry of impairment. The diagnosis should be considered in any child with acute or subacute unexplained ataxia, cranial nerve palsies, weakness or pain in the trunk and/or limbs. Patients with Guillain-Barré syndrome may be misdiagnosed as having encephalitis (which may also accompany the Guillain-Barré syndrome), myositis, cachexia, arthralgia, arthritis, transverse myelitis, behaviour disorder, or hysteria. Prominent cranial nerve involvement may lead to an apparent absence of brainstem reflexes and be misinterpreted as coma, particularly if accompanied by limb paralysis. The Miller-Fisher variant may present with cranial nerve involvement ataxia and proprioceptive loss without detectable motor weakness.

The differential diagnosis of subacute polyneuropathy includes glue sniffing, diphtheria, botulism, heavy metal poisoning, poliomyelitis, organophosphate poisoning, myasthenia gravis (tick paralysis), and rabies.

The series of Rantala *et al* is similar to others in reporting the need for assisted ventilation in between 10–20% of cases. Such severely affected cases have an appreciable mortality. Meticulous intensive nursing and medical care are essential for proper management.[5] Pneumonia, autonomic instability, pulmonary embolism, hyponatraemia, and encephalopathy are well recognised complications. Cardiac arrest, particularly precipitated by external stimuli, such as tracheal suction, was reported by Cole and Matthew[6] in five of 11 patients (including two with a more chronic polyneuropathy) requiring ventilation. In the presence of substantial fluctuations in blood pressure, central venous pressure monitoring is essential, particularly as excessive sweating and disturbed gut function may also increase parenteral fluid requirements. Oral fluids should be avoided because of the risk of aspiration and consequent respiratory failure. Total paralysis without impairment of awareness can be a terrifying experience: reassurance and good communication with the patient are therefore especially important. Sedatives may be helpful, although cardiovascular and respiratory side effects may be potentiated by the neuropathy.

Although disability after recovery is exceptional in children (and in most adult series), plasmapheresis has been justified in non-ambulant adults on the grounds that it speeds recovery and shortens the duration of hospital stay substantially.[4] Epstein and Sladky reported a mean time to independent ambulation of 25·4 days in nine children treated with plasmapheresis compared with 60·2 days in 14 historical controls.[7] In that study, only one child in each group required ventilation. However, plasmapheresis has its own morbidity, particularly when applied to infants. Steroids are not helpful and may predispose to relapse.[5] Recently, intravenous gammaglobulin has been reported to be helpful in Guillain-Barré syndrome by Kleyweg *et al*,[8] and subsequently by Shahar *et al*,[9] using doses ranging from 0·4–1 g/kg/day in a small number of children. Further controlled studies are needed before routine use of these treatments can be recommended for childhood Guillain-Barré syndrome.

In summary, Rantala and colleagues report that Guillain-Barré syndrome is uncommon and that complete recovery is the rule. However, there may be an unmeasured mortality in undiagnosed cases: a high index of suspicion is required.

C R KENNEDY
Department of Child Health,
Southampton General Hospital,
Shirley, Southampton SO9 4XY

1 Bak P. Guillain-Barré syndrome in a Danish country. *Neurology* 1985;35:207–11.
2 Larsen JP, Kvale G, Nylano H. Epidemiology of the Guillain-Barré syndrome in the county of Hordaland, West Norway. *Acta Neurol Scand* 1985;71:43–7.
3 Schonberger LB, Hurwitz ES, Katona P, *et al.* Guillain-Barré syndrome: its epidemiology and association with influenza vaccination. *Ann Neurol* 1981;9(suppl 1):31–8.
4 The Guillain-Barré Syndrome Group. Plasmapheresis and acute Guillain-Barré Syndrome. *Neurology* 1985;35:1096–104.
5 Hughes RAC, Kadlubowski M, Hufschmidt A. Treatment of acute inflammatory polyneuropathy. *Ann Neurol* 1981;9 (suppl):125–33.
6 Cole CF, Matthew DJ. Prognosis in severe Guillain-Barré syndrome. *Arch Dis Child* 1987;62:288–91.
7 Epstein MA, Sladky JT. The role of plasmapheresis in childhood Guillain-Barré syndrome. *Ann Neurol* 1990;28:65–9.
8 Kleyweg RP, van der Meché FG, Meulstee J. Treatment of Guillain-Barré syndrome with high dose gammaglobulin. *Neurology* 1988;38:1639–41.
9 Shahar E, Murphy EG, Rolfman CM. Benefit of intravenously administered immune serum globulin in patients with Guillain-Barré syndrome. *J Pediatr* 1990;116:141–4.

The Herbst triad

Gastro-oesophageal reflux may present in unusual ways. Perhaps the most unusual is Sandifer's syndrome[1] but asthma and recurrent apnoea in infancy are well known. A report in the *Journal of Pediatric Surgery* (P Sacker, U G Stanffer, 1990;25: 1238–9) describes two children with another unusual syndrome, previously unknown to me, the Herbst triad. This consists of finger clubbing, hypoproteinaemia due to protein losing enteropathy, and gastro-oesophageal reflux but it could be expanded to a tetrad with the addition of severe iron deficiency anaemia.

The clubbing and the hypoproteinaemia resolved after fundoplication suggesting that the enteropathy is secondary to the reflux. The mechanism is not known but the authors suggest that gastro-oesophageal reflux may lead to an alteration in gut flora which in turn might cause the enteropathy. Some of the patients have the head and neck movements of Sandifer's syndrome. Who will tell me the cause of the clubbing?

ARCHIVIST

1 Kinsbourne M. Hiatus hernia with contortions of the neck. *Lancet* 1964;i:1058–61.
2 Herbst JJ, Johnson DG, Oliveros MA. Gastro-oesophageal reflux with protein-losing enteropathy and finger clubbing. *Am J Dis Child* 1976;130:1256–8.

Archives of Disease in Childhood 1991; **66**: 710–712

Miller-Dieker syndrome with ring chromosome 17

N Sharief, J Craze, D Summers, L Butler, C B S Wood

Abstract
A girl presented at 6 weeks of age with failure to thrive and arching of the back. She had various dysmorphic features, hepatosplenomegaly, and developmental delay. The electroencephalogram and cranial ultrasound were abnormal, and a computed tomogram showed lissencephaly and apparent agenesis of the corpus callosum. Because of frequent aspiration she became oxygen dependent. She later developed intractable convulsions and died at the age of 9 months.

Miller described two and Dieker *et al* described four infants all of whom had microcephaly, developmental delay, hypotonia, opisthotonos, micrognathia, ear anomalies, and lissencephaly.[1 2] Other non-consistent features included seizures, bitemporal grooving of a high forehead, anteverted nares, cardiac defects, and undescended testes. The eponym Miller-Dieker syndrome was proposed by Jones *et al*.[3]

Dobyns *et al* described three patients and reviewed five additional patients from the literature, all of whom had Miller-Dieker syndrome and an abnormality of 17p.[4] They proposed that monosomy of distal 17p may be the cause of

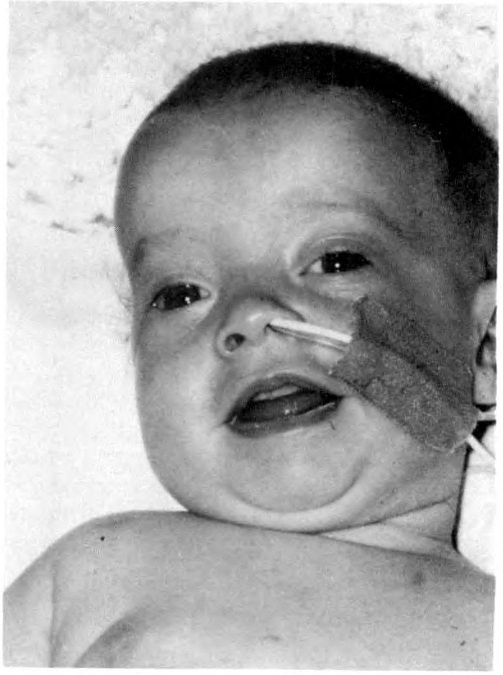


Figure 1 Facial appearance of the present case.

small with anteverted nostrils, and the jaw was

[redacted]

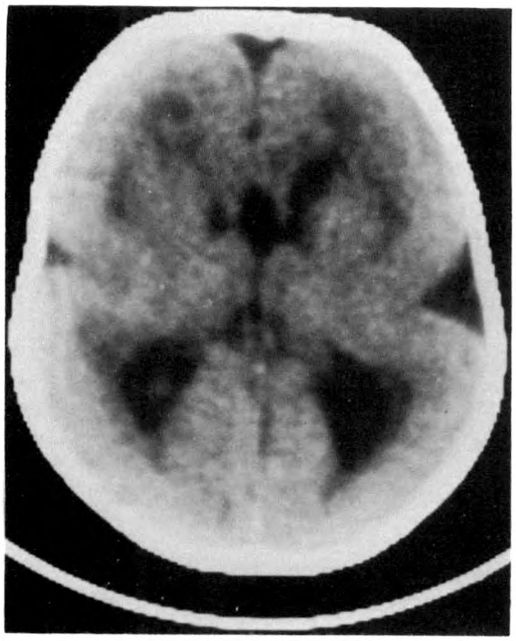


Figure 2 Computed tomogram showing a smooth cortex with absence of normal gyral pattern (lissencephaly). The lateral ventricles are widely separated with the third ventricle reaching up in between them suggesting agenesis or hypoplasia of the corpus callosum.

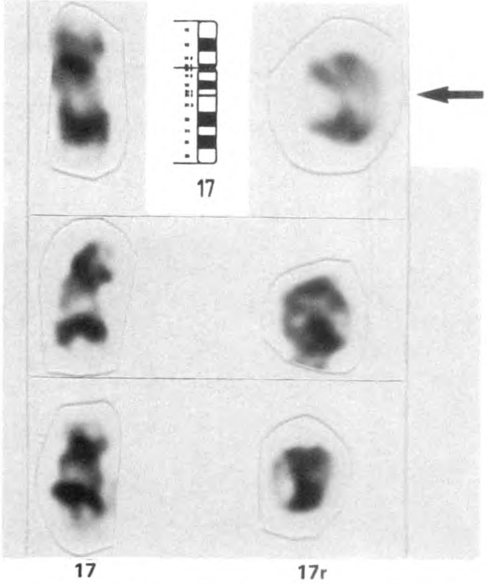


Figure 3 Homologues of chromosome 17 from three cells. The arrow indicates the site of union of the short and long arms in the ring formation, indicating only a small terminal deletion of each arm.

age was just below the third centile. She developed a divergent squint but examination of the eyes, including the corneas and fundoscopy, was normal. Her development remained static, compatible with that of a floppy newborn baby. Her convulsions started at 15 weeks of age and progressed with increasing frequency in spite of treatment with different anticonvulsants. She developed cafe au lait spots at 6 months. At 8 months her fits became intractable, and she died when she was 9 months old.

At postmortem examination there were signs of bronchopneumonia. The brain was small and agyric with a thin corpus callosum. The cortical ribbon was three times the normal thickness, the white matter was meagre, and within it were numerous nodular grey heterotopias surrounding the ventricles. Other features were small frontal and large occipital horns, dentate dysplasia and grey heterotopias in the cerebellum, and inferior olivary heterotopia in the medulla.

CYTOGENETIC STUDIES

Standard chromosome preparations were obtained from short term cultures of lymphocytes stimulated with phytohaemagglutinin in Iscove's medium. Higher banding resolution was achieved by incorporating ethidium bromide into the culture medium and exposing the slides briefly to trypsin before Giemsa staining in the usual way.

The chromosome count was 46 with a karyotype in which one of the chromosomes 17 was replaced by a ring structure (46, XX, (r) (17)). The size of the ring and the relative position of bands q24·3 and p12 indicated that the break points were probably at p13·1 and q25·3 prior to the fusion leading to the ring formation (fig 3). There is thus a terminal deletion of both long and short arms, the short arm deletion being of equivalent size to that found in the Miller-Dieker syndrome. The karyotypes of both parents were normal.

Discussion

Stratton *et al* reviewed the cytogenetics of the 11 reports of Miller-Dieker syndrome: nine showed monosomy for the terminal region of 17p down to band p13.[9] No deletion was present in one (case 2 reported by Dobyns *et al*[4]), and in another family (Norman *et al*[10]) where parental chromosomes were normal, the affected subjects did not have the typical Miller-Dieker syndrome facies.[9] To the above nine cases can be added the 12 year old boy with typical facies and terminal 17p deletion reported recently by Selypes and Laszlo.[11] In this case lissencephaly was also shown on the computed tomogram. Stratton *et al* concluded from the extent of the various deletions for 17p that the critical region for Miller-Dieker syndrome is the sub band p13·3.[9] More recently, application of DNA probes has provided substantial evidence to support this. Schwartz *et al*, and Van Tuinen *et al*, have shown that there are submicroscopic deletions of this sub band in patients with Miller-Dieker syndrome who were previously thought to have had normal chromosomes.[12,13]

There are to our knowledge five previous reports of liveborn patients with non-mosaic ring chromosome 17.[4-8] The 20 week fetus with r(17) described by Weinberg *et al* and the 4 year old girl with mental retardation and growth failure found to be a mosaic 46XX/46XX,r(17) by Petit and Koulischer are excluded from this discussion.[14,15] In addition, the report by Burdea *et al* (who described a father and son with apparent ring chromosome 17, the son being microcephalic and with mental retardation) will not be considered here as the identity of the chromosome was not confirmed by banding.[16]

These five patients had enough clinical abnormalities in common for a 'ring 17 chromosome' syndrome to be proposed by Carpenter *et al.*[7] The most common features are mental and motor retardation, growth retardation, microcephaly, flattened nasal bridge, anteverted nostrils, epicanthus, clinodactyly, hypotonia, seizures, cafe au lait spots, and a transverse palmar crease. The patients of Dobyns *et al* and Chudley *et al* with ring 17 reinforced this impression with further evidence that loss of material from chromosome 17 was the cause of this clinical appearance.[4,8] Two of the cases also had lissencephaly, but only one had a defective corpus callosum.[4,7] The break points in their ring chromosomes must therefore render them monosomic for the critical region distal to 17p12. The patients of Ono *et al*, Qazi *et al*, and Chudley *et al* had neither lissencephaly nor a typical Miller-Dieker syndrome phenotype suggesting that the short arm region including 17p13 was almost entirely preserved in them.[5,6,8] A comparison of the clinical features of ring 17 phenotype and Miller-Dieker syndrome is shown in table 1, together with the clinical details of the present case.

Our patient exhibited features of both ring chromosome 17 (psychomotor and growth retardation, microcephaly, flat nasal bridge, anteverted nares, fits and cafe au lait patches), and of Miller-Dieker syndrome (lissencephaly, antenatal and postnatal growth retardation, bitemporal hollowing, anteverted nares, long philtrum, thin upper lip, micrognathia, fits, and developmental delay). Chromosome analysis confirmed the presence of r(17) with breakpoints indicating that she was monosomic for the Miller-Dieker syndrome critical region 17p13·3. She also had hypoplasia of the corpus callosum similar to cases 1 and 3 reported by Dobyns *et al.*[4] The agenesis of the corpus callosum has been reported in a girl with partial deletion of distal 17q.[17] Our patient and case 1 of Dobyns *et al* were also monosomic for distal 17q but case 3 of Dobyns *et al* with t(7:17) translocation was not, as the q arm was not affected.[4] It is unlikely therefore that monosomy 17q is the only determining factor for this congenital malformation of the brain. Our patient had nodular heterotopia within the white matter and bilateral olivary heterotopia of the medulla, as previously reported.[1,2,10]

Comparison of clinical features of present case, Miller-Dieker syndrome, and ring chromosome 17

Clinical features	*Miller-Dieker syndrome*	*Ring chromosome 17*	*Present case*
Growth retardation	Yes	Yes	Yes
Mental retardation	Yes	Yes	Yes
Microcephaly	Yes	Yes	Yes
Lissencephaly	Yes	No	Yes
Prominent occiput	Yes	No	No
Narrow forehead/excessive wrinkled skin	Yes	No	Yes
Hypertelorism	Yes	Yes	Yes
Epicanthus	No	Yes	No
Palpebral fissures slanting downwards	Yes	No	Yes
Ptosis	Yes	No	No
Divergent squint	No	No	Yes
Clouded cornea	Yes	No	No
Small nose	Yes	No	Yes
Broad nasal bridge	No	Yes	Yes
Prominent bulbous nose	No	Yes	No
Anteverted nostrils	Yes	Yes	Yes
Puckered lips	Yes	No	Yes
Malformed ears	Yes	Yes	Yes
Ears rotated posteriorly	Yes	No	Yes
Micrognathia	No	Yes	Yes
High arched palate	No	Yes	No
Widely spaced nipples	No	Yes	No
Arachnodactyly	No	Yes	No
Low set thumbs	No	Yes	No
Polydactyly	Yes	No	No
Coxa vara	No	Yes	No
Abnormal palmar creases	No	Yes	Yes
Cafe au lait spots	No	Yes	Yes
Hirsutism	Yes	Yes	No
Hypotonia	Yes	Yes	Yes
Seizures	Yes	Yes	Yes
Heart defect	Yes	Yes	No
Renal defect	Yes	No	No

In conclusion, we have presented a case in which the features of Miller-Dieker syndrome and r(17) were present. As far as we know it is the first case reported from the United Kingdom.

We thank Dr Brian Harding, department of histopathology, Hospital for Sick Children, for undertaking the neuropathological examination, and Mrs Gloria Parkin for preparing the manuscript.

1 Miller JQ. Lissencephaly in two siblings. *Neurology* 1963;**13**: 841–50.

2 Dieker H, Edwards RH, ZuRein G, Chou SM, Hartman HA, Opitz JM. The lissencephaly syndrome. *Birth Defects* 1969; **5**:53–64.

3 Jones KL, Gilbert EF, Kaveggia EG, Opitz JM. The Miller-Dieker syndrome. *Pediatrics* 1980;**66**:277–81.

4 Dobyns WB, Stratton RF, Parke JT, Greenberg F, Nussbaum RL, Ledbetter DH. The Miller-Dieker syndrome: lissencephaly and monosomy 17p. *J Pediatr* 1983; **102**:552–8.

5 Ono K, Suzuki Y, Fujii I, Takeshita K, Arima M, Nagakome Y. A case of ring chromosome E-17:46XXr(17) (p13–q25). *Japanese Journal of Human Genetics* 1974;**19**:235–42.

6 Qazi QH, Madahar C, Kanchanapoomi R, Giridharan R, Beller E. Ring chromosome 17 in a mentally retarded boy. *Ann Genet (Paris)* 1979;**22**:234–8.

7 Carpenter NJ, Leichtman LG, Stamper S, Say B. An infant with ring 17 chromosome and unusual dermatoglyphics: a new syndrome? *J Med Genet* 1981;**18**:234–6.

8 Chudley AE, Pabello PD, McAlpine PJ, Nickel BE, Shokeir MHK. Ring chromosome 17 in a mentally retarded young man—clinical, cytogenic and biochemical investigations. *Am J Med Genet* 1982;**12**:219–25.

9 Stratton RF, Dobyns WB, Airhart Susan D, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. *Hum Genet* 1984;**67**:193–200.

10 Norman MG, Roberts M, Sirios J, Tremblay LJM. Lissencephaly. *Can J Neurol Sci* 1976;**3**:39–46.

11 Selypes A, Laszlo A. Miller-Dieker syndrome and monosomy 17p13: a new case. *Hum Genet* 1988;**80**:103–4.

12 Schwartz CE, Johnson JP, Holycross B, *et al.* Detection of submicroscopic deletions in band 17p13 in patients with Miller-Dieker syndrome. *Am J Hum Genet* 1988;**43**: 597–604.

13 VanTuinen P, Dobyns WB, Rich DC, *et al.* Molecular detection of microscopic and submicroscopic deletions associated with the Miller-Dieker syndrome. *Am J Hum Genet* 1988; **43**:587–96.

14 Weinberg AG, Bair JL, Harrod MJ. Ring chromosome 17 detected by amniocentesis. *Humangenetik* 1975;**28**:269–72.

15 Petit K, Koulischer L. Etude d'une mosaique 46XX/ 46XX17r. *Ann Genet (Paris)* 1971;**14**:55–8.

16 Burdea M, Lupascu E, Margineanu L. Un caz familial de chromozom din grupa e in inel (17) r cu transmitere de la tata la fiu. *Rev Med Chir Soc Med Nat Iasi* 1973;**77**:353–7.

17 Bridge J, Sanger W, Mosher G, *et al.* Partial deletion of distal 17q. *Am J Med Genet* 1985;**21**:225–9.

Archives of Disease in Childhood 1991; **66:** 713–717

Thrombosis in systemic lupus erythematosus: a French collaborative study

Marcela A Montes de Oca, Marie Claude Babron, Olivier Blétry, Michel Broyer, Victor Courtecuisse, Jean Loup Fontaine, Chantal Loirat, Jean-Philippe Méry, Philippe Reinert, Bertrand Wechsler, Micheline Levy

U155 INSERM,
Château de Longchamp,
Bois de Boulogne,
75016 Paris,
France
Marcela A Montes de Oca
Marie Claude Babron
Micheline Levy

Service de
Médecine Interne,
Groupe Hospitalier La
Pitié-Salpetrière,
Paris,
France
Olivier Blétry
Bertrand Wechsler

Service de
Néphrologie Pédiatrique,
Groupe Hospitalier
Necker-Enfants Malades,
Paris,
France
Michel Broyer

Département de
Pédiatrie,
Hôpital de Bicêtre,
Paris,
France
Victor Courtecuisse

Service de Pédiatrie,
Hôpital Trousseau,
Paris,
France
Jean Loup Fontaine

Service de
Néphrologie Pédiatrique,
Hôpital Robert Debré,
Paris,
France
Chantal Loirat

Service de Néphrologie,
Hôpital Bichat,
Paris,
France
Jean-Philippe Méry

Service de Pédiatrie,
Hôpital Intercommunale
de Creteil,
Paris,
France
Philippe Reinert

Correspondence to:
Dr Montes de Oca.

Accepted 21 January 1991

Abstract

A retrospective study was undertaken of 120 children with systemic lupus erythematosus (SLE) seen in Paris and its immediate suburbs who fulfilled at least four of the American College of Rheumatology diagnostic criteria for SLE, and in whom the disease was diagnosed before the age of 16 and between January 1975 and December 1987. Eleven of these children (eight girls and three boys) all more than 10 years of age (mean follow up 8·1 years; range 3–13) had thrombotic episodes (9%). Thrombosis was one of the presenting signs in seven patients; in five it was associated with typical symptoms of SLE, and in the other two the thrombotic episode was isolated and diagnosis of SLE was delayed one and three years. Of a total of 16 thrombotic episodes (six of which were recurrent), 14 involved the leg veins, and in four there was associated pulmonary embolism. There were two episodes that affected cerebral arteries. The American College of Rheumatology diagnostic criteria for SLE as well as the incidence of lupus anticoagulant, positive direct Coombs test, and vasculitis in this group of patients was compared with the incidence in patients with SLE but no thrombosis. Only lupus anticoagulant was significantly associated with thrombotic episodes: eight of 11 (73%) of patients with SLE and thrombotic (arterial or venous) episodes had lupus anticoagulant compared with only 10 of 74 patients (14%) with no history of thrombotic events in the same age group.

Arterial and venous thrombosis in the absence of certain risk factors (infection, operations, and vascular abnormalities) are exceptional in children. Case reports have been published about thrombotic episodes in children with systemic lupus erythematosus (SLE).[1–7] Because large series of children with SLE hardly mention thrombotic complications it is not possible to evaluate their prevalence or associated clinical and laboratory features in this age group. Venous and arterial thromboses are important in adult SLE, but it is difficult to evaluate their incidence because series are not always comparable. In a prospective study, Alarcon Segovia *et al* followed up 500 patients with SLE and found that 43 had thrombophlebitis (recurrent in 14) and 16 had arterial occlusions.[8] The leg veins were the most commonly reported site.[9] Arterial thromboses are less common, and they usually affect the intracranial or extracranial cerebral arteries, in particular the territory supplied by the middle cerebral artery.[10]

In this paper we report the incidence of thrombotic episodes in a large series of children with SLE, and examine other clinical and laboratory features of SLE that may occur in association with these episodes.

Patients and methods

In 1986 we began a collaborative study of patients who fulfilled at least four of the diagnostic criteria for SLE as defined by the American College of Rheumatology,[11] as well as the following conditions: patient admitted to hospitals in Paris or its immediate suburbs (departments 92, 93, and 94) in whom the disease was first diagnosed before the age of 16 and between January 1975 and December 1987. Drug induced disease was excluded. Given the nature of the French health system we can assume all children with SLE were admitted to hospital at least once and were therefore recorded in our study. Of the 120 patients who fulfilled these conditions 11 patients presented with thrombotic episodes and are described in detail. Because all patients with thrombotic episodes were between 10 and 16 years of age, their clinical and laboratory features were compared with those of 81 patients who did not develop thrombosis in the same age range. The significance of differences between groups was calculated by the χ^2 test with Yates's correction.

In addition, we describe two interesting patients with thrombotic episodes who were thought to have SLE. They are excluded from our SLE group because we applied the American College of Rheumatology criteria strictly and they fulfilled only two or three of them.

Routine and immunological laboratory studies were done in different laboratories of the various hospitals, using standard techniques, and included antinuclear antibodies, anti-DNA antibodies, positive lupus erythematosus cell preparation, presence of antibodies to extractable nuclear antigens (ribonucleoprotein antigen or RNP, Sm antigen, Ro/Sjögren syndrome A antigen or Ro/SSA, La/Sjögren syndrome B antigen or La/SSB) and direct Coombs test. In addition, a false positive syphilis serology was ascertained when the Venereal Disease Research Laboratory reaction was positive and the *Treponema pallidum* haemagglutination or the fluorescent treponemal absorption test were negative.

On initial admission before treatment, most children had had complete coagulation profiles done including prothrombin time, kaolin cephalin clotting time (KCCT), platelet count, and individual factor assays. If either the prothrombin time or KCCT were prolonged, the presence of lupus anticoagulant was detected by measuring KCCT on a 1:1 mixture of citrated patient's plasma and pooled normal plasma. The presence of lupus anticoagulant was confirmed if a prolonged KCCT was not corrected by mixing it 1:1 with pooled normal plasma, which would be the case if the prolonged KCCT was the result of a deficit in coagulation factors.

Results

CLINICAL AND LABORATORY FEATURES OF PATIENTS WITH SLE AND THROMBOTIC EPISODES

Eleven patients (eight girls and three boys) had at least one thrombotic episode (tables 1 and 2). All were over 10 years of age (mean age 11·8) and had a mean follow up of 8·1 years (range 3–13 years). Two girls were sisters (cases 6 and 7); they have been mentioned elsewhere.[3]

In seven children the thrombosis was one of the presenting symptoms. In five it was associated with typical symptoms of SLE, while in two it was isolated, and the diagnosis of SLE was only made one year (case 3) and three years (case 11) after the onset of disease. Six patients had only one thrombotic episode each, but five had more than one: recurrent venous thrombosis (n=4), venous thrombosis and pulmonary embolism (n=2), and arterial and venous thrombosis (n=1). Of a total of 16 thrombotic episodes, 14 were in leg veins, and in four instances they were associated with pulmonary embolism. Two affected the territory of the middle cerebral arteries. Nine patients had venous thrombosis of leg veins: superficial veins (n=5), both superficial and deep veins (n=2), and deep veins (n=2). Deep venous thrombosis was confirmed by phlebography and pulmon-

Table 1 Clinical characteristics of 11 patients with systemic lupus erythematosus who developed thromboses

Case No	*Sex*	*Age at onset of disease (years)*	*Thrombosis*		*Other clinical signs*	*Follow up (years) and outcome*
			Site	*Time after onset of disease (years)*		
1	M	11·0	Superficial vein, left lower leg (two episodes)	1·3 and 7·6	Oral ulcers, vasculitis, pleural effusion, thrombocytopenia, leucopenia, proteinuria (focal glomerular nephritis)	10·0, clinical remission
2	M	14·1	Deep leg veins Left femoropopliteal Left iliofemoralpopliteal	 4·5 7·2	Malar rash, vasculitis, pancytopenia, nephrotic syndrome (proliferative glomerular nephritis)	6·3, clinical remission
3	F	10·1	Superficial femoral vein and pulmonary embolism	At onset	Photosensitivity, polyarthritis, leucopenia	4·5, clinical remission
4	F	13·8	Deep and superficial iliofemoral veins	At onset	Malar rash, photosensitivity, vasculitis	3·2, clinical remission
5	F	11·6	Right iliofemoral vein and pulmonary embolism	2·6	Malar rash, vasculitis, photosensitivity, polyarthritis	10·5, clinical remission
6	F	10·7	Superficial right leg vein	At onset	Oral ulcers, Raynaud's disease, vasculitis, arthritis, pericarditis, thrombocytopenia, leucopenia, proteinuria	3·8, death
7	F	11·9	Superficial lower leg vein and pulmonary embolism Deep iliofemoral vein	At onset 5·8	Vasculitis, polyarthritis, proteinuria proliferative glomerular nephritis, fetal death at 30 weeks	11·9, clinical remission
8	F	10·4	Superficial left leg vein	1·8	Malar rash, nephrotic syndrome (proliferative glomerular nephritis)	10·9, death
9	F	11·4	Superficial right leg vein (two episodes) and pulmonary embolism	At onset	Haemolytic anaemia, thrombocytopenia, proteinuria (membranous glomerular nephritis)	13·5, clinical remission
10	F	11·8	Inferior vena cava and left iliofemoral vein Left middle cerebral artery territory	At onset 8·0	Malar rash, right side paraesthesiae	12·0, clinical remission
11	M	14·3	Right middle cerebral artery territory	At onset	Malar rash, thrombocytopenia, leucopenia, proteinuria, left hemiplegia, choreic like movements, headaches, left hypoacousia, dysarthria	3·0, death

Table 2 Laboratory features in 11 patients with systemic lupus erythematosus and thrombosis and in control subjects

Case No	*Anti-DNA antibody*	*Antinuclear antibody*	*Antibodies to extractable nuclear antigens present*	*False positive serology for syphilis*	*Coombs test*	*Lupus anticoagulant*
1	Yes	Yes	Sm	ND	Yes	Yes
2	Yes	Yes	No	No	No	No
3	Yes	Yes	Ro/SSA	No	Yes	Yes
4	Yes	Yes	No	Yes	Yes	Yes
5	Yes	Yes	ND	Yes	Yes	Yes
6	Yes	Yes	La/SSB	Yes	Yes	Yes
7	Yes	Yes	No	Yes	Yes	Yes
8	Yes	Yes	ND	ND	No	No
9	Yes	Yes	ND	ND	Yes	No
10	Yes	Yes	Sm	No	ND	Yes
11	No	No	No	Yes	Yes	Yes
Patients without thrombosis	104/108	109/109	Sm 20/82	8/47	38/79	13/100

ND, not done.

ary embolism by isotopic lung scanning. One patient (case 10) had both arterial and venous lesions and one (case 11) had exclusively arterial thrombosis.

At onset case 10 presented with thrombosis of both the inferior vena cava and the left iliofemoral vein. Arterial thrombosis was presumed because cerebral computed tomography showed an ischeaemic lesion (area of hypodensity) in the left thalamic region eight years after onset and the patient had right sided paresthesiae. Arteriography was not done.

The other case of arterial thrombosis (case 11) presented at the onset of SLE with thrombosis of both superficial sylvian arteries that was confirmed by carotid arteriography. Computed tomography of the brain showed ischaemic lesions of the right tempororolandic area. He had episodes of occipital and temporal headaches associated with choreic type abnormal movements of his right side that preceded left hemiplegia, difficulties in pronunciation, diminution of visual acuity in the lower visual quadrants, and a left hearing deficit. He recovered the use of his left side, but continued to have headaches associated with visual impairment and abnormal choreic type movements of the right side. Apart from the initial overt infarction within the territory of the middle cerebral artery, transient ischaemic attacks might explain the severe headaches and the transitory visual impairments with which he presented. He died of acute pancreatitis presumably related to SLE, though an infective cause cannot be excluded. He was the only patient who lacked 'typical' anti-DNA and antinuclear antibodies.

Three patients (cases 1, 2, and 6) had haemorrhagic syndromes that presented with purpura and ecchymosis. All had severe thrombocytopenia (platelet count less than $100\times10^9/l$).

Lupus anticoagulant was found in eight of the 11 patients (table 2). In most of them it was repeatedly measured and found either to persist or to become positive after several years of follow up. There was only one exception (case 6) in whom it became negative three years after onset of disease.

All the patients with SLE received comparable doses of steroids when the disease was diagnosed; patients with thromboses also received anticoagulants. At the time of writing eight of the patients were in remission (table 1). Three patients died, though none from complications of their thrombotic episodes: one died of pancreatitis (case 11), one of myocarditis (case 6), and one of rupture of the arterial suture immediately after renal transplantation (case 8). This patient was the only one with thrombotic episodes who developed end stage renal failure.

When the incidence of vasculitis, lupus anticoagulant, positive Coombs test, and the presence of American College of Rheumatology diagnostic criteria for SLE in this group of patients was compared with that among patients without thrombotic complications, the only significant difference was in the presence of a lupus anticoagulant: eight of 11 (73%) of patients with SLE and thrombotic (arterial or venous) episodes had lupus anticoagulant, compared with only 13 of 100 patients who had no thrombotic episodes ($p<0{\cdot}001$). Nine patients in our series did not have coagulation profiles done.

THROMBOTIC EPISODES IN TWO PATIENTS WITH LESS THAN FOUR CRITERIA FOR SLE

Two patients with less than four American College of Rheumatology criteria for SLE (one boy and one girl) presented with thrombotic episodes. The boy had non-painful swelling of his left lower limb and phlebography showed chronic thrombotic occlusion of the popliteal, femoral, and saphenous veins. In addition, he had anti-DNA antibodies, false positive serology for syphilis, thrombocytopenia, and positive lupus anticoagulant. Treated with hydroxychloroquine, he is doing well after 10 years follow up.

The girl presented with thrombocytopenia, positive lupus anticoagulant, false positive serology for syphilis, low titres of anti-DNA antibodies, anaemia with a positive direct Coombs test, and primary acute adrenal insufficiency in addition to deep venous thrombosis of lower limbs. Antibodies against adrenal tissue were not determined and an adrenal venogram was not done. She was treated with cortisone and fludrocortisone and at the time of writing was doing well after nine years of follow up.

Discussion

Eleven children (9%) in our series of 120 patients with SLE had single or recurrent thrombotic episodes. Most of the episodes were venous. Thrombotic episodes in the absence of certain risk factors are uncommon in children, and the diagnosis of SLE must be considered. Inherited factors predisposing to thrombosis, however, must also be evaluated. In our retrospective study protein S and protein C concentrations in plasma were not determined and antithrombin III deficiency was not investigated.

Children with SLE and thrombotic episodes have only been described in case reports to our knowledge. Olive *et al* described a 9 year old boy who had extensive thrombosis of the inferior vena cava and femoral veins associated with thrombocytopenia and haemolytic anaemia as the presenting sign of SLE.[1] St Clair *et al* described a 14 year old boy with painless swelling of his right thigh; SLE was subsequently confirmed.[2] Bernstein *et al* discussed two girls aged 10 and 14 who presented with recurrent venous thrombosis and positive lupus anticoagulant.[4] The first patient had confirmed SLE with deep venous thrombosis of the lower extremities, and the older one had positive anti-DNA antibodies and false positive serology for syphilis associated with Budd-Chiari syndrome and superficial thrombosis of the leg veins. A boy aged 12, one of the children described by Pelkonen *et al*, presented with thrombosis of the femoral vein, pulmonary embolism, thrombocytopenia, anti-DNA antibody and lupus anticoagulant.[5] He developed obvious SLE three years later. All these patients had positive lupus anticoagulant and were treated with anticoagulants in addition to corticosteroids. A 5 year old girl reported by Appan *et al* had SLE with haemolytic anaemia as the presenting symptom followed a year later (when corticosteroid treatment was interrupted) by multiple arterial thromboses of the brain and retina and peripheral venous thrombosis of both hands and feet. She had a positive lupus anticoagulant.[6] Recently renal artery thrombosis and hypertension with positive lupus anticoagulant were reported in a 13 year old girl with SLE.[7] She also had neurological symptoms and a computed tomogram suggestive of cerebral thrombosis. She was treated with prednisone, antihypertensive drugs, and anticoagulants and her condition was satisfactory. No deaths were reported by these authors. In our series three patients died, none from complications of their thrombotic episodes.

We also described two other patients with thrombotic episodes who did not fulfill the American College of Rheumatology criteria for SLE. One of them presented with adrenal insufficiency. Case reports of thrombotic complications in young patients with lupus anticoagulant without clear cut SLE are rare. Kelley and Berger reported a 16 year old girl with a right middle cerebral occlusion and deep venous thrombosis of the lower limbs associated with lupus anticoagulant, false positive syphilis serology, and antinuclear antibodies, but who had less than four of the criteria for SLE.[12] Two boys aged 12 and 13 years old were described by Ravelli *et al*; they had deep venous thrombosis associated with anticardiolipin antibody and lupus anticoagulant.[13] One had low titres of antinuclear antibody. Pelkonen *et al* reported on a 10 year old girl with thrombosis of the vena cava and both iliac veins who had initially presented with adrenal insufficiency.[5] Apart from these only adult case reports have associated acute adrenal insufficiency with recurrent deep venous thrombosis and antiphospholipid antibodies.[14 15] As to the aetiology and pathogenesis, the reported absence of antibodies to adrenal tissue seems to negate the autoimmune hypothesis, and the possibility of bilateral adrenal vein thrombosis should be considered. In our patient with adrenal insufficiency, antibodies against adrenal tissue were not measured, and as the possibility of venous thrombosis was not suspected at the time, an adrenal venogram was not done.

In our series a significant number of the children with SLE and thrombotic episodes had positive lupus anticoagulant compared with those who had no history of thrombosis. Adult series have extensively documented this association since Bowie *et al* first described it in 1963.[16] The lupus anticoagulants are a spontaneously acquired population of antibodies (IgM, IgG) initially described in SLE patients[17] that interfere with in vitro phospholipid dependent coagulation reactions.[18] Bleeding is uncommon in the absence of associated severe thrombocytopenia, qualitative platelet defects, hypoprothrombinaemia, or coagulation factor deficiencies.[19] The lack of standardisation and the differing sensitivities of various assays to detect lupus anticoagulant, as well as differences in patient populations, make comparisons between different studies difficult and probably account for incidences that vary from 6–18%[19] to 40–50%.[20] In our series, 21/111 (19%) of our patients with SLE had lupus anticoagulant. At present, diagnosis of lupus anticoagulant should be strengthened by confirmatory studies using the tissue thromboplastin inhibition test, the dilute Russell viper venom time, or the platelet neutralisation procedure.[21] The anticardiolipin antibody was not measured in our retrospective series. It is a sensitive test for the detection of antiphospholipid antibodies, and its determination is becoming increasingly important.

Several hypotheses were reviewed in a recent paper to try to explain the relationship between antiphospholipid antibodies and thrombosis, but at present it cannot be said if lupus anticoagulant is the cause, the result, or an epiphenomenon of thrombosis.[21] Given the phospholipid specificity of lupus anticoagulant, alterations in either endothelial or platelet membrane functions would seem the most likely explanations for lupus anticoagulant induced thrombotic complications. It has been hypothesised that lupus anticoagulant may increase coagulant properties by decreasing anticoagulant systems that depend on the endothelium.[21] The affinity of the lupus anticoagulant for phospholipids might explain its reported association with thrombocytopenia,[9] and false positive syphilis reactions.[19] Lupus anticoagulant fixation on phospholipid membranes might lead to peripheral destruction. Cross reactions with the cardiolipin antigen used in Venereal Disease Research Laboratory reactions might explain the high percentages of false positive serology for syphilis in patients with lupus anticoagulant.

In adult series, a syndrome consisting of a tendency to recurrent thrombosis together with recurrent mid-pregnancy fetal loss,[22] thrombocytopenia, haemolytic anaemia,[23] livedo reticularis,[24] valvular heart disease,[10 25 26] and chorea associated with antibodies against phospholipids, has been proposed.[27 28] Severe migrainous headaches may antedate other cerebral vascular symptoms.[29] Case 11 with arterial thrombotic episodes had had severe headaches five years before diagnosis of disease.

Alarcon Segovia *et al* argue that patients with and without SLE but who have at least two features significantly associated with the presence of anticardiolipin antibodies (venous thrombosis, thrombocytopenia, haemolytic anaemia, leg ulcers, or recurrent fetal loss) in addition to antiphospholipid antibodies, should be included in a antiphospholipid syndrome.[8] The identification of a more homogeneous subset of patients might provide new insights into the pathophysiology and the treatment of the antiphospholipid syndrome and of SLE as well.

Our reported incidence of thrombosis in childhood onset SLE is rarely reflected in published reports, but merits attention. Even if currently required standardised procedures for determining lupus anticoagulant were not entirely satisfied, given the retrospective nature of our study, our data are strongly suggestive of a relationship between lupus anticoagulant and thrombosis in SLE in childhood. Though there is at present no test that can predict which patients will actually develop symptoms, lupus anticoagulant (or anticardiolipin antibodies, or both) should be determined to screen patients at risk for thrombotic complications (including recurrent abortions in older female patients). Data accumulated so far do not justify therapeutic interventions on the basis of the presence of a lupus anticoagulant alone, and in our series long term anticoagulant treatment was avoided in children with thrombotic episodes because of the haemorrhagic risk during play and sport. An increasing number of patients with lupus anticoagulant with or without clear cut SLE are, however, receiving long term treatment with low doses of aspirin to reduce the risk of recurrent thrombosis.[25 29]

The study was supported by MGEN contract number 3926, Paris, France.

1 Olive D, André E, Brocard O, Labrude P, Alexandre P. Lupus érythémateux disséminé revélé par des thrombophlébites des membres infériurs. *Arch Fr Pediatr* 1979;**36:** 807–11.

2 St Clair W, Jones B, Rogers JS, Crouch M, Hrabovsky E. Deep venous thrombosis and a circulating anticoagulant in systemic lupus erythematosus. *Am J Dis Child* 1981;**135:** 230–2.

3 Perraudin ML, Rousseau A, Desbois LC, Herrault A, Lévêque B. Thromboses veineuses, anticoagulant circulant et lupus erythémateux disséminé. A propos de 2 cas chez 2 sœurs HLA identiques. *Ann Pediatr (Paris)* 1981;**28:**251–9.

4 Bernstein ML, Salusinsky-Sternbach M, Bellefleur M, Esseltine DW. Thrombotic and hemorrhagic complications in children with the lupus anticoagulant. *Am J Dis Child* 1984;**138:**1132–5.

5 Pelkonen P, Simell O, Rasi V, Vaarala O. Venous thrombosis associated with lupus anticoagulant and anticardiolipin antibodies. *Acta Paediatr Scand* 1988;**77:**767–72.

6 Appan S, Boey ML, Lim KW. Multiple thromboses in systemic lupus erythematosus. *Arch Dis Child* 1987;**62:** 739–41.

7 Ostuni PA, Lazzarin P, Pengo V, Ruffatti A, Schiavon F, Gambari P. Renal artery thrombosis and hypertension in a 13 year old girl with antiphospholipid syndrome. *Ann Rheum Dis* 1990;**49:**184–7.

8 Alarcon Segovia D, Delezé M, Oria CV, *et al.* Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. *Medicine* 1989;**68:**353–65.

9 Lechner K, Pabinger-Fasching I. Lupus anticoagulants and thrombosis. A study of 25 cases and a review of the literature. *Haemostasis* 1985;**15:**254–62.

10 Asherson RA, Lubbe WF. Cerebral and valve lesions in SLE: association with antiphospholipid antibodies. *J Rheumatol* 1988;**15:**539–43.

11 Tan EM, Cohen AS, Fries JF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25:**1271–7.

12 Kelley RE, Berger JR. Ischemic stroke in a girl with lupus anticoagulant. *Pediatric Neurology* 1987;**3:**58–61.

13 Ravelli A, Caporali R, Bianchi E, *et al.* Anticardiolipin syndrome in childhood: a report of two cases. *Clin Exp Rheumatol* 1990;**8:**95–8.

14 Asherson RA, Hughes GRV. Recurrent deep vein thrombosis and Addison's disease in 'primary' antiphospholipid syndrome. *J Rheumatol* 1989;**16:**378–80.

15 Carette S, Jobin F. Acute adrenal insufficiency as a manifestation of the anticardiolipin syndrome? *Ann Rheum Dis* 1989;**48:**430–1.

16 Bowie EJW, Thompson JH, Pascuzzi CA, Owen CA. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. *J Lab Clin Med* 1963;**62:** 416–30.

17 Conley CL, Hartmann RC. A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. *J Clin Invest* 1952;**31:**621–2.

18 Feinstein DI, Rappaport SI. Acquired inhibitors of blood coagulation. *Prog Hemost Thromb* 1972;**1:**75–95.

19 Shapiro SS, Thiagarajan P. Lupus anticoagulants. *Prog Hemost Thromb* 1982;**6:**263–85.

20 Derksen RHWM, Hasselaar P, Blokzijl L, Gmelig Meyling FHJ, de Groot PG. Coagulation screen is more specific than the anticardiolipin antibody ELISA in defining a thrombotic subset of lupus patients. *Ann Rheum Dis* 1988;**47:** 364–71.

21 Triplett DA, Brandt JT. Lupus anticoagulants: misnomer, paradox, riddle, epiphenomenon. *Hematologic Pathology* 1988;**2:**121–43.

22 Lubbe WF, Liggins GC. Lupus anticoagulant and pregnancy. *Am J Obstet Gynecol* 1985;**153:**322–7.

23 Delezé M, Oria CV, Alarcon-Segovia D. Occurrence of both hemolytic anemia and thrombocytopenic purpura (Evan's syndrome) in systemic lupus erythematosus. Relationship to antiphospholipid antibodies. *J Rheumatol* 1988;**15:** 611–5.

24 McHugh NJ, Maymo J, Skinner RP, James I, Maddison PJ. Anticardiolipin antibodies, livedo reticularis and major cerebrovascular and renal disease in systemic lupus erythematosus. *Ann Rheum Dis* 1988;**47:**110–5.

25 Chartash EK, Lans DM, Paget SA, Qamar T, Lockshin MD. Aortic insufficiency and mitral regurgitation in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am J Med* 1989;**86:**407–12.

26 Ford PM, Ford SE, Lillicrap DP. Association of lupus anticoagulant with severe valvular heart disease in systemic lupus erythematosus. *J Rheumatol* 1988;**15:**597–600.

27 Harris EN, Hughes GRV, Gharavi AE. Antiphospholipid antibodies: an elderly statesman dons new garments. *J Rheumatol* 1987;**14:**208–13.

28 Hughes GRV, Harris KN, Gharavi AE. The anticardiolipin syndrome. *J Rhematol* 1986;**13:**486–9.

29 Asherson RA, Khamashta MA, Gil A, *et al.* Cerebrovascular disease and antiphospholipid antibodies in systemic lupus erythematosus, lupus-like disease, and the primary antiphospholipid syndrome. *Am J Med* 1989;**86:**391–9.

Addendum

Since the submission of this article a girl, aged 10·5 years at onset of SLE, presented with thrombosis of a superficial lower leg vein 13 years later. She had initially presented with malar rash, polyarthritis, vasculitis, positive lupus erythematosus cell preparation, direct Coombs test, antinuclear and anti-DNA antibodies. No lupus anticoagulant was initially done.

Archives of Disease in Childhood 1991; **66**: 718–721

Perinatal hepatitis B virus infection caused by antihepatitis Be positive maternal mononuclear cells

Hiroko Shimizu, Toshihiro Mitsuda, Shinji Fujita, Shumpei Yokota

Abstract

To investigate the infectivity of hepatitis B virus (HBV) from mothers to their newborn offspring, HBV-DNA in plasma and peripheral mononuclear cells from 28 antihepatitis Be positive, hepatitis B surface antigen positive carrier mothers was examined by a highly sensitive polymerase chain reaction/Southern hybridisation technique. HBV specific DNA was detected in three maternal mononuclear cell samples, but was absent in plasma. Two of four infants born to the three mothers with HBV-DNA positive mononuclear cells developed acute or fulminant hepatitis within three months after birth. Two infants were effectively prevented from infection with HBV by combined hepatitis B immunoglobulin/HBV vaccine administration. The 25 infants born to the HBV-DNA negative mothers were free of HBV infection within the next seven months to 3·5 years. These results suggest that latent infection with HBV in maternal mononuclear cells is responsible for perinatal HBV infection.

Since the establishment of the national project for prevention of mother to infant transmission of hepatitis B virus (HBV) with hepatitis B immunoglobulin (HBIg) and HBV vaccine, approximately 90–95% of the offspring of hepatitis Be antigen (HBeAg) positive HBV carrier mothers acquired protection from perinatal infection in Japan.[1 2] In contrast, prophylaxis is not recommended for infants of HBeAg negative mothers, who comprise three quarters of pregnant hepatitis B carriers. About 10% of infants born to such mothers are reported to develop acute or fulminant hepatitis.[3] As half of the cases of infantile fulminant hepatitis are due to perinatal HBV infection, and because most mothers of these patients are HBeAg negative, hepatitis B surface antigen (HBsAg) positive carriers,[3] protective measures for these infants are urgently needed.

Although the infectivity of HBV is conventionally monitored by noting the presence of HBeAg and by measuring the activity of HBV specific DNA polymerase, recent advances in molecular hybridisation technology have provided more sensitive markers of HBV infection.[4 5] HBV-DNA can be detected even in anti-HBe positive sera,[6] and regardless of HBeAg status, the quantity of circulating HBV-DNA is directly related to HBV infectivity and to the activity of chronic liver disease.[7 8] However, any mechanisms of HBV transmission from HBeAg negative, HBsAg positive carrier mothers to their babies have never been documented.

In the present study, to explore the infectivity of anti-HBe positive, HBsAg positive carrier mothers to their offspring the expression of HBV-DNA was determined in plasma and peripheral mononuclear cells by a newly developed method, the polymerase chain reaction. Coupled with molecular hybridisation analysis the polymerase chain reaction can define attogram concentrations of HBV-DNA.[9] The present results demonstrate the close association between the HBV-DNA expression in maternal peripheral mononuclear cells and the onset of acute or fulminant hepatitis in early infancy.

Subjects and methods

The serological markers of HBV infection were detected by reverse passive haemagglutination for HBsAg, passive haemagglutination for anti-HBs, immunoadherence haemagglutination for antibody to hepatitis B core antigen, and enzyme linked immunosorbent assay for HBeAg and its antibody (Abbott Laboratories).

We examined 28 mothers known to be anti-HBe positive, HBsAg positive carriers and 29 of their infants. The mothers were asymptomatic, without liver function abnormalities, during a one to five year follow up. All infants studied were negative for HBsAg and anti-HBs in cord blood, and serum HBsAg and anti-HBs concentrations and transaminase activities were measured every three months until age 1 year. At birth and at 2 months of age two infants were given HBIgs (pepsin digested Cohn fraction II HBIg, 200 IU/ml, provided by the Japanese Red Cross Central Blood Centre, Tokyo). They were also given HBV vaccine (HBsAg:10 μg protein/2·5 ml, Kitasato Institute, Tokyo) at 3, 4, and 6 months of age.

Samples of heparinised peripheral blood were layered onto Ficoll-Hypaque (Oncor Inc), and plasma and mononuclear cells were separated by centrifugation. Mononuclear cells were washed twice in phosphate buffered saline and then were immediately frozen at −80°C. DNA preparation, DNA amplification, and gel separation/Southern hybridisation methods have been previously described.[9] Briefly, DNA was amplified in a 100 μl reaction mixture that contained 10 μl sample DNA, 2·5 units *Taq* DNA polymerase, 200 μmol of each deoxynucleotide triphosphate (dATP, dCTP, dTTP, and dGTP), 1 μmol of each primer (primer 114: 5'-ACAGAGTCTAGACTCGTGGT-3', primer 586R:5'-AAAGCCCTACGAACCACTGA-3'), 50 mmol/ml potassium chloride, 10 mmol/l

Department of Paediatrics, Yokohama City University School of Medicine, Japan
Hiroko Shimizu
Toshihiro Mitsuda
Shumpei Yokota

Yokohama City Maternity Hospital (Aiji Centre)
Shinji Fujita

Correspondence to:
Dr Shumpei Yokota,
Department of Paediatrics,
Yokohama City University School of Medicine,
3–9, Fukuura,
Kanazawa-ku,
Yokohama 236,
Japan.

Accepted 18 January 1991

TRIS-hydrochloric acid (pH8·3), 1·5 mmol/l magnesium chloride, and 0·01% gelatin. Amplification in a programmable thermal cycler (Techne) consisted of 25 cycles at 94°C for one minute (denaturation), 58°C for two minutes (annealing), and 72°C for three minutes (extension). Amplified DNA samples were fractionated by 1% agarose/2% Nusieve (FMC Bio-Products) gel electrophoresis, and the DNA was visualised by ultraviolet fluorescence after staining with ethidium bromide. After Southern blotting to 'Hybond N' membranes (Amersham), blots were hybridised with a cloned HBV-DNA probe labelled by random primed incorporation of digoxigenin labelled deoxyuridine triphosphate (Boehringer Mannheim). Alkaline phosphatase conjugated antibody to digoxigenin was then applied to the membrane and the colorimetric reaction was carried out on the membrane.

Results

HBV markers including HBsAg, anti-HBs, HBeAg, and anti-HBe, and transaminase activities of 28 carrier pregnant women at or shortly before delivery were determined. All sera were HBeAg negative and anti-HBe positive, and none showed evidence of active hepatitis. During the next one to five years, serological markers and transaminase activities of these women were essentially unchanged. The HBV infection status of each father was also determined, and no evidence of infection was obtained (data not shown).

DNA was extracted from 200 μl of plasma and 10^6 mononuclear cells of the mothers categorised as above. Each DNA was amplified by 25 cycles of the polymerase chain reaction. A sample was regarded as positive when DNA with a molecular weight expected for the amplified product (473 base pairs) was seen in agarose/Nusieve gel in three independent experiments. Southern hybridisation was used to confirm the specificity of the amplified DNA.

All of the 28 plasma samples were negative by both direct visualisation of amplified DNA and by Southern hybridisation, even when increased amounts of DNA were applied in the polymerase chain reaction mixture. In contrast, 473 base pair bands were detected in three of 28 mononuclear cell DNA samples (fig 1). The HBV specificity of these amplified DNAs was con-

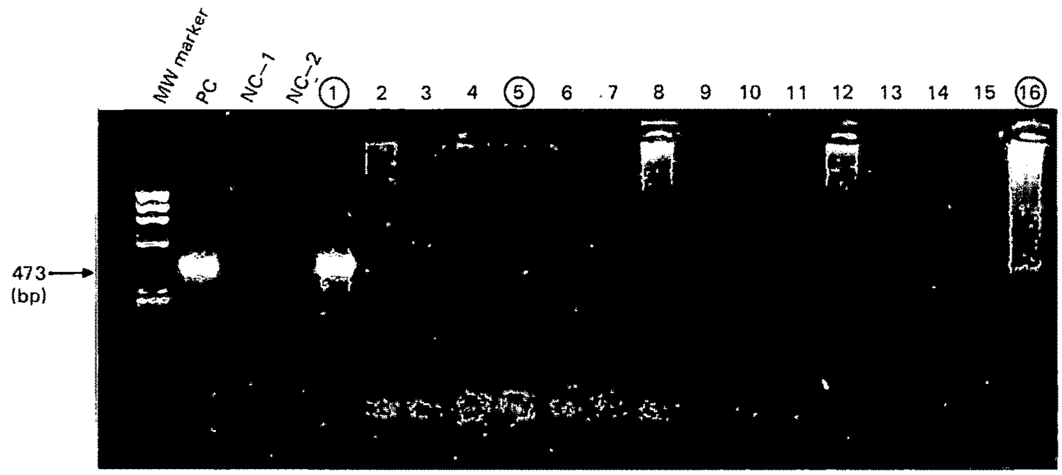


Figure 1 Detection of HBV-DNA in peripheral mononuclear cells obtained from anti-HBe positive, HBsAg positive carrier mothers. Molecular weight (MW) marker, X174/Hae III digest; PC:positive control, HBV-DNA 3·2 kilobase pairs (kbp) template amplified with HBV primers; NC-1:negative control, Perkin-Elmer Cetus DNA amplification kit DNA template with HBV primers; NC-2:negative control, HBV-DNA 3·2 kbp template with Cetus kit primers. DNA in peripheral mononuclear cells was extracted as described in subjects and methods, and amplified with Taq enzyme in the presence of HBV primers. Amplified DNA was separated in 1% agarose/2% Nusieve gel.

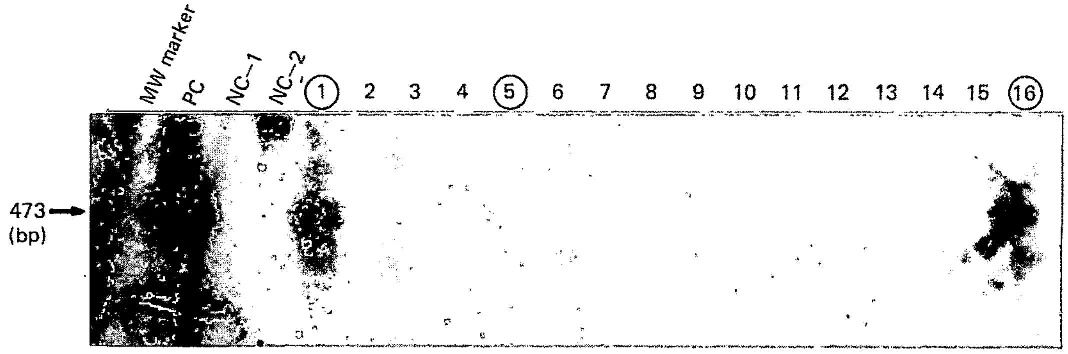


Figure 2 Polymerase chain reaction and Southern hybridisation anaylsis of HBV-DNA in peripheral mononuclear cells obtained from anti-HBe positive, HBsAg positive carrier mothers. Molecular weight (MW) marker, PC:positive control, NC-1 and 2: negative controls. The DNA in the gel shown in fig 1 was transferred to nylon membrane and hybridised with digoxigenin-11-dUTP-labelled HBV-DNA (Dig-ELISA).

Detection of HBV-DNA by the polymerase chain reaction (PCR)

Case No	*Mothers*									*Infants (prognosis, whether infected or not)*	
	Serum					*Plasma*		*Mononuclear cells*			
	*HBsAg**	*HBs* antibody*	*HBc* antibody*	*Aspartate amino-transferase†* *(IU/l)*	*Alanine amino-transferase†* *(IU/l)*	*PCR+ ethidium bromide staining*	*PCR+ Southern blot hybridisation*	*PCR+ ethidium bromide staining*	*PCR+ Southern blot hybridisation*		
1	13	–	11	23	19	–	–	++	+	Fulminant hepatitis; died	Sisters
	11	–	12	19	19	–	–	++	+	Given HBIg/HBV vaccine; no infection	
5	9	–	14	23	7	–	–	+/–	+	Given HBIg/HBV vaccine; no infection	
16	11	–	16	32	28	–	–	+	+	Acute hepatitis (aspartate aminotransferase 319 IU/l, alanine aminotransferase 245 IU/l)	

*HBsAg by reverse passive haemagglutination (titre=2^n); HBs antibody by passive haemagglutination; and HBc antibody by immunoadherence haemagglutination (titre=2^n).

†Normal activities: aspartate aminotransferase <35 IU/l; alanine aminotransferase <30 IU/l.

firmed by Southern hybridisation (fig 2). The remaining 25 mononuclear cell DNA samples were negative by both DNA gel analysis and hybridisation (partly shown in figs 1 and 2).

The HBV markers and transaminase activities of the offspring were serially determined. Among the four infants born to the three mothers who carried HBV-DNA positive mononuclear cells, two developed acute or fulminant hepatitis within three months after birth (table). In the infant with acute hepatitis anti-HBs, and later anti-HBc, became positive, confirming HBV infection. One of the remaining two infants, who was the younger sister of the girl who died from fulminant hepatitis, was administered HBIg/HBV vaccine, and acquired protection against HBV as her anti-HBs was positive and anti-HBc negative after prophylaxis. The last one of the four was also administered HBIg/HBV vaccine because her mother seroconverted from HBeAg positive to anti-HBe positive shortly before delivery (between 29 and 36 weeks of gestation), and the infant also acquired HBV protection (table). In the other 25 infants, whose mothers were HBV-DNA negative in both plasma and mononuclear cells, no HBV markers and no increased activities of transaminases were detected in the next seven months to 3·5 years. Taken together these results strongly suggests that the association between the HBV-DNA expression in maternal peripheral mononuclear cells and the HBV infection of their infants is highly specific.

Discussion

The present study demonstrates that even asymptomatic, anti-HBe positive pregnant women may carry HBV-DNA positive mononuclear cells in the peripheral blood that can transmit infectious HBV to their offspring. This is the first report concerning the association between the presence of HBV-DNA in maternal mononuclear cells and the onset of infantile hepatitis. In Japan 1–2% of pregnant women are HBsAg positive carriers and three quarters of them are HBeAg negative. This percentage of HBV carriers seems relatively high, but the prevalence of HBV in Japan is about 20 times more than in Europe. Therefore it is important to pick up high risk infants and to find the most effective means of treatment. Our findings indicate that HBV determination in peripheral mononuclear cells of such pregnant women will aid screening of high risk infants before delivery.

Infectivity of HBV was apparently due to mononuclear cells in maternal peripheral blood. In order to acquire the capability of viral replication, the infected mononuclear cells are probably transmitted first as intact cells to the infants, and then the HBV is activated. The possible route of mononuclear cell transmission could be transplacental passage around delivery. Previously, Desai and Creger reported that the maternal mononuclear cells definitely circulate in newborn babies.[10] They labelled in vitro the maternal peripheral mononuclear cells by immunofluorescence and injected them back into the mother shortly before delivery. They detected the labelled maternal mononuclear cells in the infant's circulation. Very recently the transfer of mononuclear cells from fetus to mother was determined by the polymerase chain reaction. Y chromosome specific DNA sequences were detected in pregnant women carrying male fetuses.[11] These findings strongly suggested that bidirectional mononuclear cell traffic between mother and fetus is not uncommon. Therefore, it is most likely that HBV carrying maternal mononuclear cells traverse the placenta intact. But other routes of HBV transmission, for example horizontal infection after birth, are possible. Further studies are needed.

It was surprising that, though the women were asymptomatic, acute or fulminant hepatitis could occur in the infants. The HBs antigenaemia in these anti-HBe positive women might at least indicate active translation of viral DNA, which is the final step of HBV expression, suggesting that an immunological inactivation process is operating in the women. Such a mechanism might be too immature and thus unable to protect the infants from viral activation. The direct link between HBV and lymphoid cells was very recently established.[12] The evidence for the replication of HBV in peripheral mononuclear cells derives from the demonstration that a 3·4–3·5 kb RNA transcipt was detected by northern blot analysis in mononuclear cells that expressed HBsAg on their surface,[13] and that 1–10% lymphocytes obtained from HBsAg positive, HBeAg negative chronic carriers contained viral RNA by in situ hybridisation.[14]

Our findings will also be relevant to the prevention of infantile fulminant hepatitis. Although one child of a HBV-DNA positive mother died at 3 months from fulminant hepatitis, HBV infection was averted in the sister by the combined administration of HBIg and HBV vaccine. There must be an argument that without the combined treatment no one can predict anything about the infant's prognosis. This seems to be reasonable, but a recent trial of the prophylactic HBIg single injection to infants born to HBeAg negative, HBsAg positive carrier mothers proved effective in reducing the rate of onset of infantile hepatitis to about 20–30% of the non-treated children.[15] It is still difficult to predict the risk of fuliminant hepatitis, so it would seem prudent that infants of HBV-DNA mononuclear cell positive mothers receive treatment with both HBIg and HBV vaccine.

We thank Dr Philip L Cohen, Dr Kazufumi Tsubaki, and Dr Tetsuo Mori for helpful comments; the medical and nursing staff of Yokohama City Maternity Hospital (Aiji Centre) for their cooperation; and Shigeko Yamaguchi for laboratory assistance. This study was supported by grants from a local specialised studies subsidy from Yokohama City.

1 Tada H, Yanagida M, Mishina J, *et al.* Combined passive and active immunization for preventing perinatal transmission of hepatitis B virus carrier state. *Pediatrics* 1982;**70**:613–9.

2 Kanai K, Takehiro A, Noto H, *et al.* Prevention of perinatal transmission of hepatitis B virus (HBV) to children of e antigen-positive HBV carrier mothers by hepatitis B immune globulin and HBV vaccine. *J Infect Dis* 1985;**151**: 287–90.

3 Shiraki K, Tanimoto K, Yamada K, *et al.* Hepatitis B virus infection in the infants born to HBe antigen negative carrier mothers: a preliminary report. *Acta Paediatrica Japonica* 1986;**28**:338–41.

4 Bonino F, Hoyer B, Nelson J, Engle R, Verme G, Gerin J. Hepatitis B virus DNA in the sera of HBsAg carriers: a marker of active hepatitis B virus replication in the liver. *Hepatology* 1981;**1**:386–91.

5 Scotto J, Hadchouel M, Hery C, Yvart J, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in serum by a simple spot hybridization technique: comparison with results for other viral markers. *Hepatology* 1983;**3**:279–84.

6 Negro F, Chiaberge E, Oliviero S, *et al.* Hepatitis B virus DNA (HBV-DNA) in anti-HBe positive sera. *Liver* 1984;**4**: 177–83.

7 Carloni G, Delfini C, Colloca S, Alfani E, Tallani G, DeBac C. Incidence of hepatitis B virus DNA in DNA-polymerase in sera of Italian asymptomatic carriers with the serological markers of HBV. *Arch Virol* 1986;**87**:97–105.

8 Kam W, Rall LB, Smuckler EA, Schmid R, Rutter WJ. Hepatitis B viral DNA in liver and serum of asymptomatic carriers. *Proc Natl Acad Sci USA* 1982;**79**:7522–6.

9 Mitsuda T, Yokota S, Mori T, *et al.* Demonstration of mother-to-infant transmission of hepatitis B virus by means of polymerase chain reaction. *Lancet* 1989;**ii**:886–8.

10 Desai RG, Creger WP. Maternofetal passage of leukocytes and platelets in man. *Blood* 1963;**21**:665–73.

11 Lo YMD, Patel P, Wainscoat JS, Sampietro M, Gillmer MDG, Fleming KA. Prenatal sex determination by DNA amplification from maternal peripheral blood. *Lancet* 1989; **ii**:1363–5.

12 Lamelin JP, Trepo C. The hepatitis B virus and the peripheral blood mononuclear cells: a brief review. *J Hepatol* 1990;**10**:120–4.

13 Colucci G, Jacobson I, Lalatta F, Vernance S, Waksal SD, Weksler ME. Detection of hepatitis B virus DNA, RNA and surface antigen in mononuclear cells from patients with type B hepatitis. *Clin Res* 1986;**34**:648A.

14 Hadchouel M, Pasquinelli C, Fournier JG, *et al.* Detection of mononuclear cells expressing hepatitis B virus in peripheral blood from HBsAg positive and negative patients by in situ hybridization. *J Med Virol* 1988;**24**:27–32.

15 Matsumoto S, Shiraki K, Morizuka T, *et al.* Prophylaxis of HB virus infection by single dose injection of HBIg in babies born to HBe-antigen negative HBV carrier mothers. *Journal of Japan Pediatric Sciences* 1989;**93**:1374–82.

Urinary infection: what little boys do in the bath

A recent paper from Quebec (J Labbé, *Pediatrics* 1990;**86**:703–6) raises an interesting new possibility as regards the aetiology of urinary infection in boys. A prospective consecutive series of 22 boys aged between 5 and 15 years who attended a urinary infection clinic at a university medical centre, together with nine others detected retrospectively, were questioned about penile self instrumentation in the bath or shower. Ten of the 31 admitted injecting bath water into the urethra in the few days before the onset of symptoms. The instruments used were a syringe ($n=4$), a rubber bulb ($n=3$), a plastic bottle ($n=2$), and a 'hand-held shower massager' ($n=1$). Lower abdominal pain, dysuria, and gross haematuria were more common in the 10 boys who admitted self instrumentation (group A) than in the 21 who didn't (group B). Urine culture in group A produced *Escherichia coli* in five and *Staphylococcus saprophyticus* in the other five. Only one child in group B was infected with the latter organism. Imaging of the renal tracts showed no abnormalities in group A but was abnormal in a third of the boys in group B.

Is this study representative? I imagine, but don't know, that such things as syringes and rubber bulbs may be less available in British bathrooms. The frequency of this behaviour in normal boys is unknown so it is difficult to assess the size of its contribution, if any, to the problem of urinary infection in boys, but it's an idea worth pursuing. No doubt we shall hear more on this subject.

ARCHIVIST

Archives of Disease in Childhood 1991; 66: 722–723

Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness

Nozomi Hosoda, Wataru Sunaoshi, Hiroyuki Shirai, Yuki Bando, Hisao Miura, Muneo Igarashi

Abstract

Anticarbamazepine antibody was detected in a patient who had clinical signs of serum sickness induced by carbamazepine. Skin rash, fever, oedema, and lymphadenopathy are classic signs of severe adverse reaction, but although immunological hypersensitivity is thought to be a contributory factor, the presence of anticarbamazepine antibody has not previously been reported to our knowledge.

Carbamazepine is widely used in the treatment of various forms of epileptic disorders.[1 2] Although different side effects have been reported, skin rash is the most common adverse reaction. Exfoliative dermatitis, urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, and a reaction similar to systemic lupus erythematosus have been reported.[2 3] In some cases the skin rash is part of a severe illness affecting several organs, and immunological hypersensitivity is thought to contribute to the skin reaction.[3 4] So far, however, we know of no report of the presence of anticarbamazepine antibody in any patient with severe skin reactions.

We present a patient with the typical clinical manifestations of serum sickness, fever, eruption with oedema (particularly around the face and neck), and lymphadenopathy. The laboratory findings showed a decrease in complement C4 and an increase in C3a and C4a activity. Anticarbamazepine antibody was detected in the serum using an enzyme linked immunosorbent assay (ELISA).

Methods

BALB/C mice were given carbamazepine (1 g/kg) orally, and bled six hours later. The serum was used as the antigen.

The anticarbamazepine antibody of serum from the patient was analysed by ELISA, a procedure that has been described elsewhere.[5] Briefly, the mouse serum diluted (1:100) with 10 mM carbonate buffer was added to 96 well polyvinylchloride microtitre plates, and left for two hours at room temperature. The nonbinding sites were blocked with phosphate buffered saline containing 0·05% Tween 20 and 2% ovalbumin. Diluted human serum was added to the wells and incubated for one hour at 4°C. After three washings, 100 µl of appropriately diluted horseradish peroxidase conjugated goat antimouse Ig antiserum was added to each well. The plates were then incubated for one hour at 4°C and washed three times, and 200 µl of freshly prepared substrate solution containing 0·05% o-phenylendiamine and 0·0075% hydrogen peroxide in McIlvain buffer, pH 6·0, was added to each well. After 30 minutes of incubation at room temperature, absorbance was read at 405 nm with a Titertek Multiskan plate reader.

Case report

An 8 year old girl was admitted with fever and skin rash. Thirty seven days before admission carbamazepine 200 mg (10 mg/kg) had been prescribed because of a complex partial seizure. Twenty seven days before admission the first skin rash had appeared on her cheeks, but this disappeared within a few days. Twenty three days before admission, the dose of carbamazepine had been increased to 300 mg. The day before admission she had again developed maculopapular erythema on her face and neck, this time accompanied by fever. Her past history and family history were not helpful. On examination she had maculopapular erythema on her face, neck, and trunk, and her body temperature was 40°C. Several bilateral cervical lymph nodes were enlarged to less than 2 cm in diameter and the liver was also enlarged. Laboratory findings on admission included aspartate aminotransferase activity 108 U/l, alanine aminotransferase activity 107 U/l, C3 1·29 g/l, C4 384 mg/l; white blood cell count, haemoglobin concentration, and platelet count were normal. Carbamazepine had been discontinued because of suspected hypersensitivity, but the high fever and skin rash persisted. A week later the facial oedema was so bad that she could not open her eyes and she had developed a productive cough. Crackles could be heard in her chest and an x ray film showed mild bronchopneumonia in the right middle lobe. She also had watery diarrhoea several times a day.

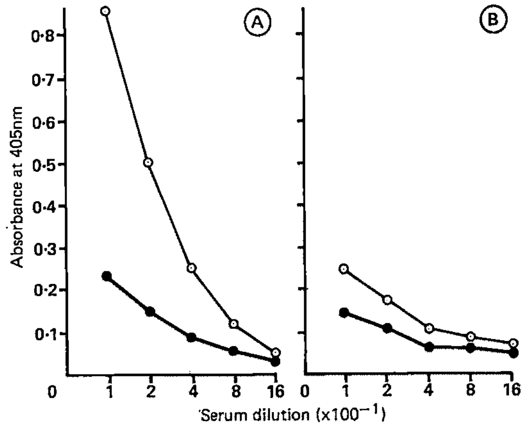
The pneumonia and the diarrhoea resolved within a few days without any special treatment, and the fever and skin rash subsided on the 15th day in hospital. Cultures of throat swabs, blood, and urine grew no pathogens. Antistreptolysin titre and Paul-Bunnell test were negative, as were other titres, including cytomegalovirus, Epstein-Barr virus, measles, rubella, and mycoplasma. Immunological findings on the 24th day in hospital were as follows: C3 1·32 g/l, C4 114 mg/l, C3a 1329 ng/ml, and C4a 827 ng/ml.

On the 26th hospital day, a patch test was done with carbamazepine, and with cephazolin as the negative control. An area of erythema with induration 1 cm in diameter was detected against carbamazepine, but there was no skin

Deparment of Paediatrics, Kitasato University School of Medicine, 1-15-1, Kitasato, Sagamihara, Kanagawa, 228, Japan
Nozomi Hosoda
Wataru Sunaoshi
Hiroyuki Shirai
Yuki Bando
Hisao Miura
Muneo Igarashi

Correspondence to: Dr Igarashi.

Accepted 18 January 1991



Titration of patient's serum (○—○) and normal human pooled serum (●—●) against mouse serum containing carbamazepine (A) and normal mouse serum (B).

reaction against cephazolin. The results of ELISA titration of the patient's serum against carbamazepine are shown in the figure. The antibody titre of the patient's serum (on the 14th hospital day) against carbamazepine was significantly higher than against normal mouse serum. This showed that the antibody activity was carbamazepine specific because the patient's serum did not bind to normal mouse serum that was used as the negative control. The antibody activity of the patient's serum against normal mouse serum was slightly higher than that of normal pooled human serum. This activity was the result of antigen non-specific binding, because the patient's immunoglobulin concentration was about three times higher than that of normal human serum.

Discussion

Adverse reactions to drugs are common, and various mechanisms are responsible for most non-immunological drug reactions. True immunological reactions probably account for at most a quarter of the overall total of adverse drug reactions.[6 7 8] Most drugs are simple chemicals with molecular weights of less than 1000, and these are rarely immunogenic. Substances of low molecular weight may act as haptens, however, and became immunogenic after covalent chemical binding with tissue or plasma proteins to form drug-protein conjugates.[8] In general, only drugs (or their degradation products or metabolites) with sufficient chemical reactivity to bind irreversibly to proteins are capable of inducing hypersensitivity reactions. After initial exposure to the drug, potentially allergic subjects have a latent period before the onset of the hypersensitivity reaction. During this seven to 10 day (up to three week) period, the drug-protein complex stimulates production of a sufficient number of activated immune effector cells and antibodies to cause the allergic reaction.[6 8] It is rational to attribute the skin rash induced by carbamazepine to an immunological disorder, because 80% of carbamazepine can bind to protein[10] and the skin rash does not appear for seven days.[1]

We have described a patient who showed the classic clinical picture of serum sickness.[7] Carbamazepine specific delayed type hypersensitivity was detected by patch test, and carbamazepine specific antibody was also detected using an ELISA. These findings showed that carbamazepine specific T cells and B cells in the patient had been stimulated and proliferated into sufficient numbers of effector cells. Anaphylatoxins were increased and complement was depressed, suggesting that complement was activated by immune complexes. From the clinical picture and the laboratory findings we deduced that this case was compatible with serum sickness caused by massive amounts of carbamazepine antibody immune complexes. The extensive expansion of the clone size of anticarbamazepine cells could be attributed to the prolonged carbamazepine sensitisation. Usually such prolonged sensitisation would not happen, because carbamazepine is discontinued as soon as the skin rash appears. The evidence presented by this case suggests that most cases of carbamazepine induced skin rash might be the result of mild serum sickness.

Another question is: why are so few people allergic to carbamazepine? We used mouse serum as the antigen, which was obtained by bleeding from mice that had been given a large amount of carbamazepine. Though large numbers of immune complexes were predicted from the clinical picture and laboratory findings, few haptenic epitopes appeared in the mouse serum because the anticarbamazepine titre was low. This observation suggests that haptenic epitopes formed from carbamazepine metabolites appear in only a few patients who suffer from the immunological hypersensitivity induced by carbamazepine. To verify this possibility, further analysis will be required.

1 Gamstop I. Treatment with carbamazepine: children. *Adv Neurol* 1975;11:237–46.
2 Sillanpää M. Carbamazepine. Pharmacology and clinical uses. *Acta Neurol Scand* 1981;64(suppl 88):9–202.
3 Robert DL, Marks R. Skin reactions to carbamazepine. *Arch Dermatol* 1981;117:273–5.
4 Permin H, Sestoft L. Deposits of plasma proteins in the skin during treatment with carbamazepine and diphenylhydantoin. *Acta Med Scand* 1977;202:113–7.
5 Igarashi M, Kashiwagi N, Ferrone S. Serological and structural heterogeneity of HLA-DR and DQ antigens in HLA-DR4 homozygous B lymphoid cells. *Kitasato Med* 1987;17:194–204.
6 Kenneth PM. Clinical spectrum of allergic and pseudo allergic drug reactions. *J Allergy Clin Immunol* 1984;74:558–66.
7 Elliot FE. Allergic disorders. In: Behrman RE, Vaughan VC, eds. *Nelson textbook of pediatrics*. 13th Ed. Philadelphia: WB Saunders, 1987:480–513.
8 Patterson R, Anderson J. Allergic reactions to drugs and biologic agents. *JAMA* 1982;248:2637–45.
9 Chesham J, Davies GE. The role of metabolism in the immunogenicity of drugs: production of antibodies to a horseradish peroxidase generated conjugate paracetamol. *Clin Exp Immunol* 1985;61:224–31.
10 Morselli PL, Frigerio A. Metabolism and pharmacokinetics of carbamazepine. *Drug Metab Rev* 1975;4:97–113.

Pulse oximetry in acute asthma

J Bishop, T Nolan

Abstract

The predictive value of pulse oximetry was evaluated in 100 patients who attended the emergency department with acute asthma. Oximetry after treatment with a cut off point of <91% had a sensitivity of 42% and specificity of 78% for unfavourable outcome, and oximetry before treatment had a sensitivity of 36% and a specificity of 57%. Despite its low sensitivity, oximetry after treatment does seem to have a role in minimising diagnostic errors in the emergency department, but only when used in conjunction with clinical assessment.

Patients presenting with acute asthma vary in their response to treatment, and the decision to admit them is usually made if they fail to respond adequately to treatment with a bronchodilator. Although severity of attack is not the sole determinant of the need for admission, if it is underestimated inappropriate discharge may result. It has recently been suggested that oximetry may be a useful predictor of the need for admission to hospital even though its sensitivity is relatively poor.[1] In this study we aimed to show whether arterial oxygen saturation (Sa_{O_2}) on arrival (either before or after initial treatment), and change in saturation in response to inhalation treatment, would predict admission, relapse, duration of inpatient stay, and duration of morbidity associated with the acute episode that was reported by parents.

Patients and methods

The study group comprised patients aged 0·5–17 years presenting to the emergency department with a clinical diagnosis of asthma. Patients without a history of asthma whose symptoms did not subsequently improve (consistent with the American Thoracic Society definition of asthma) were not included.[2]

Oximetry was carried out with an Ohmeda Biox 3700 pulse oximeter both on arrival at the emergency department and again at least 35 minutes after treatment with nebulised salbutamol. The signal strength was monitored until stable measurements were obtained.

Treatment was by inhalation of 0·5% salbutamol (1 ml diluted to 4 ml with saline) for 10 minutes by nebuliser driven by air at 8 l/minute. Inhalations were repeated after 20–30 minutes if indicated. Patients who responded to treatment (resolution of dyspnoea, wheeze, and use of accessory muscles) were sent home with instructions to continue with bronchodilator treatment, or take a short course of prednisolone in tapering doses, or both. Patients who responded inadequately were admitted to hospital. The maximum duration of emergency room treatment was five to six hours. Other factors influencing the decision to admit included distance of home from the hospital and social circumstances. All clinical assessments were made without knowledge of Sa_{O_2} measurements.

Sensitivity and specificity were calculated for the prediction of admission and also for the prediction of unfavourable outcome, which was defined as admission to hospital, or representation for medical care within five days, or parent dissatisfaction with the child's condition after the visit to the emergency room.[1]

The inpatient treatment was measured by the length of time for which the child had required nebulised salbutamol (every two hours or more often), which was noted in the hospital records. Functional impairment was measured by the parent's estimate of the total number of days that the child had been unwell, which was obtained by follow up by telephone two weeks after attendance.

Results

One hundred patients with a mean (SD) age of 5·9 (4·4) years were entered in the study. Thirty patients had oximetry carried out before treatment only; of these 10 had mild asthma and were discharged from the emergency room without receiving inhalation treatment, and two had severe attacks and were admitted immediately. Forty six patients had oximetry carried out before and after treatment, the remaining 24 had readings done after treatment only. Forty two patients were admitted at this attendance, four were sent home but returned later and were then admitted, five families stated at follow up that after discharge from the emergency department they had taken their child to a general practitioner or elsewhere for further medical care, and one parent was unhappy that the child had been discharged from the emergency department. A total of 52 patients, therefore, had an unfavourable outcome.

The mean (SD) Sa_{O_2} on arrival was 92·5 (3·50)% and was identical to that after treatment. The correlation between Sa_{O_2} after treatment and heart rate was −0·32 (p=0·008) and respiratory rate −0·37 (p=0·002).

Analysis of variance showed that there was no overall significant difference in Sa_{O_2} before treatment among patients who were discharged home, who were discharged and then admitted, or who were admitted straight away (p=0·30), or change in Sa_{O_2} after treatment (p=0·61), but the mean Sa_{O_2} values after treatment for the three groups were 93·6%, 92·7%, and 91·7%, respectively (p=0·07). The lack of overall difference in change in Sa_{O_2} concealed the fact that

Melbourne University Department of Paediatrics, Royal Children's Hospital, Parkville, Australia 3052
J Bishop
T Nolan

Correspondence to:
Dr Nolan.

Accepted 23 January 1991

(*Arch Dis Child* 1991;66:724–725).

patients with initially low Sao_2 values and little change after treatment were more likely to have an unfavourable outcome than those who did show improvement (p=0·004, fig 1).

Figure 2 shows that oximetry values before treatment are little better than chance at predicting outcome (p=0·23),[3] and that oximetry values after treatment are significantly better than chance (p=0·025), and substantially better than values before treatment (p=0·065).[4] The sensitivites and specificities of the Sao_2 values after treatment were 42% and 78% taking 91% or less of predicted normal as the cut off point, 67% and 46% taking 93% or less as the cut off point, and 72% and 43% taking 94% or less as the cut off point. The positive predictive value of the Sao_2 values after treatment taking 91% or less as the cut off point (and a prevalence of 61%) was 75%, and the negative predictive value was 46%.

Of the 46 children who had both Sao_2 values measured, 90% of those who were 91% of predicted normal or less on both occasions had an unfavourable outcome (sensitivity 45%, specificity 94%). This equates to a superior positive predictive value of 90% and a negative predictive value (similar to Sao_2 after treatment alone) of 42%.

The overall mean (SD) duration of frequent inhalations was 14·6 (11·92) hours and neither of the Sao_2 measurements predicted the duration. This result was not altered when adjustment for age was made in Cox's proportional hazard regression.

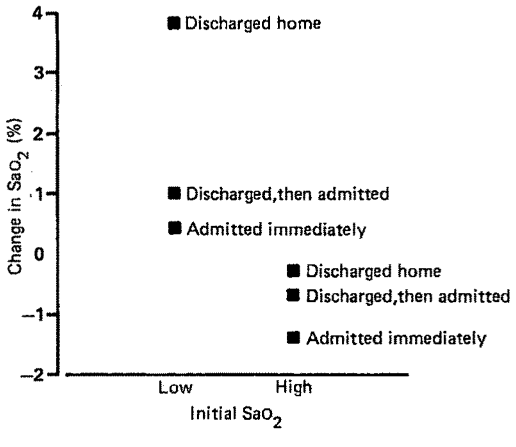


Figure 1 Changes in Sao_2 after treatment with inhaled salbutamol.

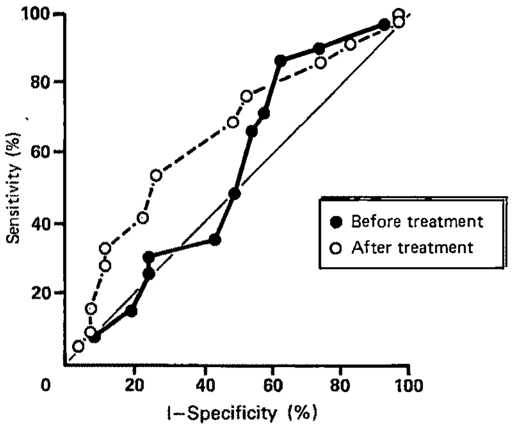


Figure 2 Sensitivity and specificity of oximetry before and after treatment with salbutamol for predicting unfavourable outcome.

The mean number of days that a child was unwell was longer (3·0 days) among those with low saturation on arrival but not significantly different from those with high saturation on arrival (1·6 days; p=0·19). The children with low saturation after treatment were unwell for a mean of 4·1 days, which was significantly longer than for those with high saturation after treatment (1·5 days; p=0·003). Adjustment for age group and sex (Cox's proportional hazard regression) confirmed that the low saturation group had 0·6 times the probability of recovering compared with children whose saturation values were above the cut off point (95% confidence interval 0·35 to 1·09).

Discussion

In emergency assessment of acute asthma, a test with high negative predictive value is desirable when the goal is to minimise the risk of inappropriate discharge. The poor sensitivity of oximetry shown in this and previous studies makes it inadequate on its own because there are too many false negative results.[1] Oximetry is a potentially useful diagnostic aid, however, if it is used in a way that takes account of its high specificity and in combination with another diagnostic test of high sensitivity. Of the many clinical severity scales studied, one with a particularly high sensitivity is the pulmonary predictive index of Skoner *et al*,[5] which is based on inspiratory breath sounds before treatment, wheezing after treatment, and the difference between respiratory rates before and after treatment. It has 95% sensitivity (and 66% specificity) for predicting the need for admission.

We calculated the value of using oximetry followed by the pulmonary predictive index for those with a negative result on oximetry before and after treatment. Assuming a prior likelihood of admission of 50%, the combined tests would achieve an overall 72% positive predictive value and 94% negative predictive value. This means that if these two tests were the criteria for decision making, we would expect 37% of all admissions to be unnecessary, but only 4% of all discharges to be inappropriate.

In summary, oximetry alone seems to be of limited value in the emergency assessment of acute asthma in children. Indeed, few would suggest that this should ever be the case. Oximetry after treatment does seem to have a role in combination with clinical assessment in minimising diagnostic errors in the emergency room.

1 Geelhoed GC, Landau LI, LeSouef PN. Predictive value of oxygen saturation in emergency evaluation of asthmatic children. *BMJ* 1988;297:395–6.
2 American Thoracic Society. Chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1962;85:762–8.
3 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36.
4 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–43.
5 Skoner DP, Fischer TJ, Gormley C, *et al*. Pediatric predictive index for hospitalization in acute asthma. *Ann Emerg Med* 1987;16:25–31.

Intussusception in cystic fibrosis

M Holmes, V Murphy, M Taylor, B Denham

Abstract

Two cases of acute intussusception in older children with cystic fibrosis are reported. Both cases presented with symptoms and signs consistent with meconium ileus equivalent, which delayed the final diagnosis. Both cases required abdominal surgery but made full and uneventful recoveries.

Intussusception occurring after the age of 2 years is relatively rare, but occurs in at least 1% of the population with cystic fibrosis.[1] We report two cases of intussusception occurring in patients with cystic fibrosis. A specific aetiology could not be found in either case.

Case reports

CASE 1

A boy was diagnosed as having cystic fibrosis at the age of 18 months by three positive sweat tests (his sweat sodium concentrations were 100, 100, and 113 mmol/l). He had been on pancreatic supplements since then with daily physiotherapy and regular courses of intravenous antibiotics. He had occasional meconium ileus equivalent, which had always settled promptly on treatment with 50 ml of oral Gastrografin (Schering, a mixture of sodium and meglumine diatrizoate). He was admitted to hospital age 10 years complaining of sudden onset of colicky abdominal pains and loose stools. Abdominal examination was normal. A plain radiograph of his abdomen showed appreciable retention of faeces consistent with meconium ileus equivalent. Gastrografin (50 ml) was given orally. The stools became more loose and more frequent over the subsequent three or four days but no relief was obtained. An abdominal ultrasound was performed which showed considerable constipation. A further 50 ml of oral Gastrografin was given. The next day the patient passed bright red blood rectally. A repeat plain radiograph of his abdomen (with the small bowel outlined by the Gastrografin) showed an obstruction at a point on the right side of the abdomen. A laparotomy was performed and an extensive ileocolic intussusception was found extending into the descending colon. The intussusception was reduced without resection. No underlying cause was found. Postoperative recovery was uneventful and the patient was discharged home two weeks later on normal diet and pancreatic supplements. There was no exacerbation of his chest condition during the illness.

The National Children's Hospital, Dublin
M Holmes
V Murphy
M Taylor
B Denham

Correspondence to:
Dr M Holmes,
7 Pembroke Street,
Dublin 4,
Republic of Ireland.

Accepted 5 February 1991
(*Arch Dis Child* 1991;66:726–727).

CASE 2

A boy was diagnosed as suffering from cystic fibrosis at the age of 6 months by three positive sweat tests (his sweat sodium concentrations were 100, 105, and 108 mmol/l). He had been on pancreatic supplements with daily physiotherapy since then and regular courses of oral antibiotics for intercurrent infections. He had a history of intermittent bouts of abdominal pain with constipation. He was admitted to hospital at age 4 years complaining of colicky abdominal pains and constipation. Abdominal examination was normal. A clinical diagnosis of meconium ileus equivalent was made. Acetylcysteine was commenced (5 ml three times a day). The patient developed loose stools of increasing frequency over the subsequent three days, but otherwise showed no symptomatic improvement. A vague mass was identified in the left upper quadrant which was thought to be faeces. This theory was supported by a plain radiograph of his abdomen. Daily bowel washouts were commenced and the patient's condition improved sufficiently over the subsequent five days for him to be discharged from hospital. The next day he was readmitted with an occurrence of the original symptoms. Examination showed a distended abdomen but nothing else. A plain radiograph of his abdomen showed a complete absence of gas in the splenic flexure and descending colon but no dilated loops of bowel or fluid levels. Abdominal ultrasound showed echogenic masses throughout the colon that were thought to be due to a faecally loaded colon. Subsequent plain radiographs of his abdomen showed dilated loops of bowel and fluid levels. A laparotomy was performed because of the acute obstruction. An ileocaecal intussusception was found with rupture of the apex of the intussusception through the wall of the sigmoid colon. A resection of bowel was performed with ileocolic anastamosis. As the sigmoid colon at the site of rupture was of doubtful viability a colostomy was fashioned with a view to later repair and closure. This was done one month later. His recovery was uneventful. He was discharged on normal diet and pancreatic enzyme supplements and the problem has not recurred.

Discussion

Acute intussusception is a common surgical problem in the first two years of life but is rarely observed in the older child.[2] It is a recognised complication in the older children who suffer from cystic fibrosis and its incidence has been put at 1% with an average age of onset between 9 and 12 years.[1] Despite this fact, it is a complication that is difficult to diagnose and is often overlooked.[3] It may present with identical symptoms to meconium ileus equivalent. Intussusception may not cause complete obstruction and although common presenting symptoms are colicky abdominal pains, vomiting and disturbance of bowel habit, absolute constipation, abdominal distention, and rectal bleeding are less commonly described.[1] Abdominal examination may be essentially normal apart from a 'faecal mass'. Bowel sound may be normal. Plain radiographs of the abdomen and abdominal ultrasound may not always be helpful in distinguishing intussusception from meconium ileus equivalent and a barium enema may be necessary. Some cases may not be diagnosed until laparotomy as in the two cases described here. Unlike intussusception in small children, hydrostatic reduction in older children is less successful and surgical reduction with or without resection is often necessary.[1 2] Apart from thick putty like material in the caecum (probably due to a combination of pancreatic enzyme deficiency and thick sticky mucus) no underlying cause is usually found.[4] It is thought that an inability of the intestine to propel the thick putty like inspissated faeces along acts as the precipitating factor.

CONCLUSION

Although intussusception is a recognised complication of cystic fibrosis it is rarely reported. It can present in a similar way to meconium ileus equivalent. This may delay diagnosis. Where a presumptive case of meconium ileus equivalent fails to respond to Gastrografin or another appropriate osmotic agent, a diagnosis of intussusception should be considered.

The authors thank Mr Prem Puri and Professor Eddie Guiney.

1 Holsclaw DH, Rockmans C, Schwachman MD. Intussusception in patients with cystic fibrosis. *Pediatrics* 1971;48: 51–8.
2 Turner D, Richwood AMK, Brereton RJ. Intussusception in older children. *Arch Dis Child* 1980;55:544–6.
3 Webb AK, Khan A. Chronic intussusception in a young adult with cystic fibrosis. *J R Soc Med* 1989;82:47–8.
4 Brown PM, Hallenbeck GA, Soule EH, Burgert EO. Cystic fibrosis with faecal retention and intussusception in late stages. *N Engl J Med* 1960;263:544–6.

Fatty infiltration in the liver in medium chain acyl CoA dehydrogenase deficiency

H C Losty, P Lee, M Alfaham, O P Gray, J V Leonard

University Hospital of Wales, Heath Park, Cardiff CF4 4XW, Department of Medical Biochemistry
H C Losty

Department of Child Health
P Lee
M Alfaham
O P Gray

Institute of Child Health, London
J V Leonard

Correspondence to:
Dr Losty.

Accepted 24 January 1991
(*ArchDisChild*1991;66:727–728).

Abstract

Fatty infiltration of the liver at postmortem examination has been recommended as a criterion for selection of infants who have died suddenly and unexpectedly for further biochemical investigation for disorders of fatty acid oxidation. We describe a boy with medium chain acyl CoA dehydrogenase deficiency who died four months after diagnosis and in whom only minimal hepatic fatty infiltration was found.

Medium chain acyl CoA dehydrogenase (MCAD) deficiency is an inherited disorder of fatty acid metabolism in which the ability to oxidise fat is impaired.[1] Patients often present within the first two years of life with hypoglycaemia, acute encephalopathy similar to Reye's syndrome and sudden, unexpected death. MCAD deficiency and the other rarer defects of fatty acid oxidation may be responsible for up to 5% of sudden, unexpected deaths in infancy (SIDS),[2] but it is not feasible to investigate all SIDS for fatty acid oxidation defects. As affected infants have had pronounced fatty infiltration of liver and muscle at postmortem examination, it has been recommended that this be used as a selection criteria.[3] We now report a patient with MCAD deficiency who died suddenly and unexpectedly four months after diagnosis. At postmortem examination only minimal fatty change in the liver was present.

Case report

This boy was the first child of unrelated parents, and he had been well until the age of 14 months when he presented with convulsions. For the previous 24 hours he had been febrile and had vomited several times. Several members of his family had diarrhoea and both *Giardia lamblia* and rotavirus were subsequently isolated from the patient's and the grandfather's stools. On admission he was unconscious with left sided focal seizures. He was hypoglycaemic (plasma glucose concentration 0·5 mmol/l) with a mild metabolic acidosis (pH 7·31, base deficit 10 mmol/l). Initially there was no hepatomegaly but during the next three days the liver became palpable 4 cm below the costal margin. His plasma ammonia concentration was 60 µmol/l. Although the aspartate transaminase activity was 204 IU/l (normal range up to 45 IU/l) and the alkaline phosphatase 1766 IU/l (normal range up to 340 IU/l), his alanine transaminase, γ-glutamyltransferase, bilirubin, and prothrombin time were normal. Electroencephalography demonstrated severe widespread abnormality with right sided focal features. He was treated with intravenous dextrose and diazepam but despite correction of the hypoglycaemia he had further convulsions over the next three days. He made a gradual recovery associated with a transient left sided weakness.

Analysis of organic acids in the urine collected on admission showed a hypoketotic dicarboxylic aciduria, and the presence of hexanoylglycine and suberylglycine was confirmed by gas chromatography-mass spectrometry. He had appreciable reduction in free and total plasma carnitine concentrations (both less than 10 μmol/l) and excreted phenyl propionyl glycine after a phenyl propionate load. MCAD deficiency was confirmed by a reduced activity of 1-^{14}C-octanoate oxidation (0·68 nmol carbon dioxide (CO$_2$)/hour/mg protein; controls 2·1–3·6 nmol CO$_2$/hour/mg protein) in cultured skin fibroblasts (G Besley, Royal Hospital for Sick Children, Edinburgh). He was discharged on treatment with phenobarbitone but despite therapeutic concentrations he continued to have fits of short duration. The family was given instructions about a high carbohydrate, low fat diet and a detailed plan about his management during any intercurrent illness.

At the age of 18 months he was found one morning convulsing in bed, no abnormality was found on admission, and he was allowed home. Two days later he became mildly unwell, vomited once, and was given several high carbohydrate drinks. He recovered during the day only to be found dead the next morning. On postmortem examination no abnormality was found. In particular frozen sections of the liver were stained for oil red 0 and showed only slight fatty change and not the panlobular steatosis that has been described.

Discussion

The poor outcome in this case emphasises the mortality associated with MCAD deficiency. However, most of the patients with MCAD deficiency who have died suddenly have a history of poor feeding during an intercurrent illness. This patient is unusual in that he received a high carbohydrate intake during his illness which, although it appeared to limit fat accumulation in the liver, did not prevent his death. It may therefore be necessary to give carnitine supplements and to continue a high carbohydrate intake during recovery from an acute illness.

An alternative explanation is that death may have been due to an epileptic fit but, although recognised as a cause of sudden, unexpected death, it is very rare in children.[4] It seems more likely that this patient died as a result of a fatty acid oxidation defect.

The absence of significant fatty infiltration of the liver has important implications for investigation of SIDS as it suggests that fatty change cannot be used as a reliable screening test to identify a high risk group likely to have a defect of fatty acid oxidation.

1 Nyhan WL. Abnormalities of fatty acid oxidation. *N Engl J Med* 1988;319:1344–6.
2 Bennett MJ, Allison F, Pollitt RJ, Variend S. Fatty acid oxidation defects as causes of unexpected death in infancy. In: Tanaka K, Coates PM, eds. *Fatty acid oxidation.* New York: Liss, 1989:349–64.
3 Editorial. Sudden infant death and inherited disorders of fat oxidation. *Lancet* 1986;ii:1073–5.
4 Dashieff RM, Dickinson LJ. Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure. *Arch Neurol* 1986;43:194–6.

General practitioner training needs for child health surveillance

L C Goodhart

Abstract

A postal questionnaire was sent to 136 Hackney general practitioners inquiring about their plans for child health surveillance. A total of 112 responded and detailed their training needs, both practical and theoretical. Ninety one responders were providing or planning to provide surveillance. Responders were eager for further training particularly in premature baby follow up, mental handicap, speech and hearing assessment, and social and behavioural problems.

Statham Grove Surgery,
Statham Grove,
Stoke Newington,
London N16 9DP
Correspondence to:
Dr Goodhart.

Accepted 21 January 1991
(*ArchDisChild* 1991;*66*:728–730).

For some years there have been proposals to develop the role of general practitioners in child health surveillance. In 1976 the Court report proposed that there should be general practitioner paediatricians,[1] but the General Medical Services Committee and the Royal College of General Practitioners felt unable to support this[2] because it undermined the strength of the general practitioner as a generalist.

As the health and development of young children are so closely related to family circumstances, it is right that child health surveillance should be regarded as part of family medicine. General practitioners can bring together preventive and therapeutic care to provide a fully integrated child health service, a concept that is now firmly supported by general practitioners and paediatricians alike. However, the inclusion of paediatric surveillance in the new contract requires evidence of additional training if general practitioners are to be remunerated for this work.

In a 1985 survey of the qualifications of, and services provided by, general practitioners in the north of England, Marsh concluded that developmental screening, and even general paediatrics, was not yet safe with general practitioners.[3] Similarly Wilmot, who questioned general practitioner trainees, showed that although 72% had worked in hospital paediatrics and 66% wanted to provide child health surveillance, only 34% felt confident to do so.[4]

After work to define the knowledge, skills, and attitudes general practitioners need to provide child health surveillance, recommendations have been made on the training objectives.[5] However, there has been little consultation with family doctors to determine their perceived educational needs.

This study was organised to ensure that proposed training courses would be tailored to local need, but the results may also reflect the needs of general practitioners nationally.

Methods

A questionnaire was sent to all Hackney general practitioners inquiring about the plans for child health surveillance services, and to discover their perceived training needs.

In Hackney, developmental checks are normally done at 6 weeks and 15 months of age by a doctor (general practitioner or community medical officer), and at 8 months and 2·5 years by a health visitor. The general practitioners were asked whether their practice provided all these preschool checks and were considered to do so whether health visitor checks were done at the surgery or a local health centre.

The doctors were asked about their qualifications, training, and experience and whether they 'felt confident' or would 'welcome further training' in 19 relevant topics.

Reminders were sent after one month and non-responders were contacted by telephone to determine whether they intended to provide child health surveillance.

Results

A total of 112 of the 136 general practitioners (82% response) including five of the seven trainees returned the questionnaire. Ninety one of the responders (including three trainees) were from practices who were providing or planning to provide child health surveillance. All other practices were successfully contacted by telephone to determine their intentions to provide child health surveillance. The 24 non-responders were spread between practices who were already providing (n=8) or planning child health surveillance (n=7), those who were not (n=7), and trainees (n=2). However, only six of the non-responders had personally applied to join the child health surveillance list.

*Table 1 General practitioners' plans to provide child health surveillance (n=129)**

	No (%) of principals
Definitely continue	49 (38)
Probably continue	3 (2)
Definitely start	27 (21)
Probably start	8 (6)
Will not start	41 (32)
Plan to stop	1 (1)

*Excludes seven trainees.

GENERAL PRACTITIONERS' INTENTIONS

All the general practitioner principals were asked whether they already provided 'all preschool checks', and whether they were likely to start or continue to provide this service in the next year (see table 1).

EXPERIENCE

Altogether 35 (38%) of the 91 responders from practices likely to provide all preschool checks had held a paediatric post with 'some training in developmental paediatrics'. For most this was during a hospital job, although some had also worked in the community. Nearly half of the doctors felt they had gained their experience in a general practitioner run child health surveillance clinic. Thirty one (34%) general practitioners had attended a postgraduate course in developmental paediatrics and 19 (21%) had the Diploma in Child Health or MRCP specialising in paediatrics (see table 2).

PERCEIVED TRAINING NEEDS

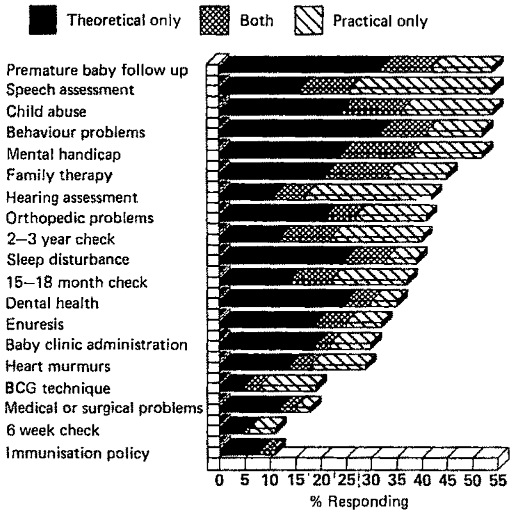
The doctors were asked whether they wanted further training in all the topics and whether this should be theoretical, practical, or both. The perceived training needs are shown in the figure as responders who wanted further training in each subject. It was interesting that the perceived training needs of doctors who had first hand experience of child health surveillance were very similar to those who had not.

Follow up of premature babies and mental handicap featured high in the list of training needs, as did the social development and behavioural problems of children. General practitioners wanted to learn more about child abuse but felt that they needed practical experience. They particularily requested practical training for speech and hearing assessment, and for the milestone checks of older preschool children. Paediatric orthopaedics and dental health promotion also stood out as gaps in knowledge.

Table 2 Experience in developmental paediatrics

	*No (%) of doctors**
Hospital paediatric job	30 (33)
Community paediatric job	15 (17)
General practitioner run child health surveillance clinic	42 (46)
Postgraduate course	31 (34)
Diploma of Child Health or MRCP in paediatrics	19 (21)

*Some doctors had more than one type of experience.



Training needs of 91 Hackney general practitioners who provided or were planning to provide child health surveillance (includes three trainees).

There was, however, relative confidence with regard to immunisations, 6 week checks, heart murmurs, and other medical and surgical problems, which were perhaps well covered by vocational training.

Discussion

This study was done in a deprived inner city area where previous training and experience in paediatric surveillance has been low compared with other parts of the country.[6] The high response rate suggests enthusiasm towards child health surveillance and an eagerness for appropriate training. General practitioners were fairly clear about the areas in which they wanted more training and opinion tended to be consistent.

As general practitioners perform more paediatric surveillance the health authority role may change, with training and advice for general practitioners becoming as important as providing clinical services. While theoretical courses can readily be tailored to address gaps in knowledge, the high demand for practical training has implications for community services. Speech therapy and audiology departments, district handicap teams, child guidance and social services could all provide training on an individual or small group basis.

The fact that so many doctors gain their experience of child health surveillance within general practice suggests that the training role of these general practice clinics should be recognised and enhanced. This could be achieved through regular support from senior community paediatricians, perhaps visiting and contributing to after clinic meetings.

The key to a successful child health programme lies in the relationship between doctors, health visitors, and others in the community health services. Multidisciplinary refresher training is one way to strengthen these links at the grass roots but such courses must address specific needs. Although this survey provides information about the topics general practitioners would wish to cover, it would be helpful to have the same information from the other professionals.

1 Committee on Child Health Services. *Fit for the future.* London: HMSO, 1976:448. (Court report.) (Cmmd 6680.)
2 Donald AG, chairman. The care of children—college policy. *J R Coll Gen Pract* 1978;**28**:553–6.
3 Marsh GN, Russell D, Russell I. Is paediatrics safe in general practitioners' hands? A study in the north of England. *J R Coll Gen Pract* 1989;**39**:138–41.
4 Wilmot JF. Preparation for paediatric surveillance. A survey of trainee general practitioners. *The Practitioner* 1984;**228**:975–7.
5 Horder JP, chairman. The paediatrics training required in the general practitioner. *J R Coll Gen Pract* 1976;**26**:128–36.
6 Burke P, Bain J. Paediatric developmental screening: a survey of general practitioners. *J R Coll Gen Pract* 1986;**36**:302–6.

Haem arginate in acute hereditary coproporphyria

D J Manning, T A Gray

Northern General Hospital, Sheffield
Department of Paediatrics
D J Manning

Department of Biochemistry
T A Gray

Correspondence to:
Dr D J Manning,
Department of Paediatrics,
Arrowe Park Hospital,
Arrowe Park Road,
Upton,
Wirral,
Merseyside L49 5PE.

Accepted 15 February 1991

(*Arch Dis Child* 1991;**66**:730–731).

Abstract

An 11 year old boy presented with severe acute hereditary coproporphyria. Despite supportive measures his condition deteriorated after admission. Haem arginate, started two days after presentation, produced appreciable inhibition of porphyrin precursor overproduction and clinical improvement.

Hereditary coproporphyria is the least common of the hepatic porphyrias. About 35% of cases present acutely.[1] Recently haem arginate, a stable haem compound, has been shown to reduce porphyrin precursor overproduction during acute attacks.[2] We report its use during severe acute hereditary coproporphyria.

Case report

An 11 year old boy was admitted after a generalised seizure. He was vomiting for nine days despite prochlorperazine and metoclopramide, and had lethargy, abdominal pain, and constipation for four days. He had eaten little in the week before admission. Apart from constipation he was previously well. His father, aged 44, had mild hypertension. Otherwise there was no significant family history.

On examination he was agitated and confused, but localising pain appropriately. Axillary temperature was 36·5 °C. The pupils were dilated but reactive, and there was no papilloedema. The ankle jerks were brisk, with clonus, and the plantar responses were equivocal. The pulse rate was 160/minute and blood pressure 150/110 mm Hg. The precordial impulse was hyperdynamic. The respiratory rate was 16/minute with shallow breaths. Abdominal examination was normal.

Investigations showed a normal peripheral white cell count and differential. Plasma urea concentration was 10 mmol/l, glucose 9·7 mmol/l, and electrolytes were normal. There was mixed respiratory and metabolic acidosis with arterial pH 7·083, carbon dioxide tension 8·27 kPa, oxygen tension 14·4 kPa, and base excess −12·9. Computed tomography of the brain was normal, and lumbar puncture showed normal cerebrospinal fluid.

Seizures persisted despite intravenous diazepam and he was given a single loading dose of intravenous phenytoin followed by a clonazepam infusion. Hypertension and tachycardia

Urine porphyrin precursors before, during, and after treatment with haem arginate. Day 0 is the day of presentation

Day	*DALA (μmol/l)*†	*Porphobilinogen (μmol/l)*†
0	758·0	355·0
1		
2*		
3*		
4*	25·6	20·2
5*	24·7	ND
6	21·0	4·7
7	42·1	5·1
8	13·7	3·1

*Indicates days on which haem arginate (100 mg) was given.
†Reference ranges: DALA, 0·8–34·3 μmol/l; porphobilinogen, 0–8·8 μmol/l.

persisted, and there was progressive diminution in level of consciousness, accompanied by dystonic posturing and loss of the gag reflex. This deterioration continued despite stopping the clonazepam. Serum sodium concentration fell from 134 to 124 mmol/l with a urine sodium of 131 mmol/l. Urine osmolality was 940 mosm/kg compared with serum osmolality 245 mosm/kg, consistent with inappropriate antidiuretic hormone secretion. Urine studies showed massively raised porphyrin precursors (table). Supportive treatment consisted of intravenous dextrose, ventilation, fluid restriction, and demeclocycline. In order to inhibit porphyrin precursor overproduction, haem arginate was started two days after admission.

There was gradual clinical improvement during the next three days, and blood pressure and pulse returned to normal. Improvement began three days after the phenytoin and 1·5 days after clonazepam was stopped. No further seizures occurred and he was successfully weaned from ventilation on the fourth day of treatment with haem arginate. There was a dramatic fall in porphyrin precursor overproduction (table) and rise in serum sodium concentration to 136 mmol/l. This improvement continued after treatment with haem arginate was stopped and three weeks after admission he was clinically normal.

Faecal coproporphyrins were raised to 320 (normally up to 46) nmol/g dry weight. Epstein-Barr virus transformed lymphocytes showed reduced coproporphyrinogen oxidase activity: 4·7 nmol carbon dioxide/hour/mg protein compared with control values (range) of 8·8 (7·4–10·3), indicating hereditary coproporphyria. Similar activities were found in lymphocytes from his brother and mother indicating that he was affected and she was the carrier.

Discussion

This boy presented with classic features of acute porphyria: abdominal pain, constipation, hypertension, encephalopathy, and inappropriate antidiuretic hormone production. Possibly phenytoin, given before the diagnosis was made, contributed to the deterioration after admission. Although hereditary coproporphyria is reputedly milder than acute intermittent porphyria, this episode was undoubtedly life threatening.

Haem production regulates, by feedback inhibition, δ-amino laevulinic acid (DALA) synthase. In acute porphyria defective haem biosynthesis results in overactivity of this enzyme. Clinical features are thought to be due to consequent overproduction of porphyrin precursors, though haem deficiency may also be relevant. For these reasons treatment with haem has been advocated. Haematin, produced by dissolving haemin in alkali, was first used. Solutions of haematin are unstable, which may have contributed to clinical ineffectiveness. In addition, haematin degradation products were implicated in side effects, including thrombophlebitis and coagulation disturbances.[3]

Recently, haem arginate has been shown to be much more stable than haematin with stability in stock solution of 96% in two years.[3] In a double blind study in 12 patients with acute intermittent porphyria, haem arginate significantly inhibited porphyrin precursor overproduction.[2] Clinical benefits were less striking, the treated group showing nonsignificant reductions in analgesic requirement, pain score, and duration of admission. The only side effect noted was mild phlebitis at the injection site in five patients. The authors suggested that the lack of statistical significance was due to the small numbers studied. They recommended that haem arginate be given to patients with severe attacks or those with peripheral neuropathy.

Porphyria commonly presents around puberty and so may present to the paediatrician. Early diagnosis and appropriate management can lead to complete remission. The most important aspects of management are removal of aggravating factors, analgesia, careful fluid balance, and intensive monitoring. For severe cases rational treatment without appreciable side effects is now available.

We thank Dr BAM Smith for permission to report this case, Professor A Goldberg for advice with managment, Dr ARW Forrest for measuring DALA and porphobilinogen, and Professor G Elder for measuring coproporphyringogen oxidase.

1 Brodie MJ, Thompson GG, Moore MR, Beattie AD, Goldberg A. Hereditary coproporphyria. *Q J Med* 1977; 182:229–41.
2 Herrick AL, McColl KEL, Moore MR, Cook A, Goldberg A. Controlled trial of haem arginate in acute hepatic porphyria. *Lancet* 1989;i:1295–7.
3 Tenhunen R, Tokola O, Linden I-B. Haem arginate: a new stable compound. *J Pharm Pharmacol* 1987;39:780–6.

Cold agglutinins in haemophiliac boys infected with HIV

P H B Bolton-Maggs, P D Rogan, J K M Duguid, K J Mutton, L M Ball

Abstract

Eleven haemophiliac boys infected with HIV were screened for irregular red cell antibodies and were compared with nine haemophiliac boys who did not have antibodies to HIV. Seven (64%) of the children who had antibodies to HIV also had cold agglutinins, mostly of anti-I specificity, compared with one (11%) of those who did not have antibodies to HIV. The children with antibodies to HIV and cold agglutinins had a significantly increased mean IgM concentration. The presence of cold agglutinins was not correlated with T4 lymphocyte count, symptoms of HIV infection, serum β_2 microglobulin concentrations, concentrations of IgG or IgA, or with the evidence of past infection with cytomegalovirus or Epstein-Barr virus.

Disturbances of immune function with hyperglobulinaemia and polyclonal activation of B cells are a feature of HIV infection.[1] Several autoantibodies have been described in infected patients including a variety of red cell antibodies.[2] These are usually of little clinical importance, although autoimmune haemolytic anaemia has been reported.[3] The presence of red cell antibodies may, however, cause problems in blood grouping and cross matching for patients requiring transfusion.

In this study a group of 11 haemophiliac children infected with HIV were screened for irregular red cell antibodies, and were compared with a group of nine HIV antibody negative haemophiliac children. Both groups had been treated with clotting factor concentrates.

Patients and methods

All haemophiliac children infected with HIV (11 boys aged 5–15 years) who were registered at Mersey regional paediatric haemophilia centre were included in the study. A sample of 5 ml clotted blood was taken, and a further 2 ml sample was placed in EDTA as part of the routine blood sampling at each visit to the clinic. The control group of patients comprised nine boys aged 2–18 years with haemophilia A or B who were attending the clinic and who had received treatment with clotting factor concentrates but who were not infected with HIV, and from whom blood was being taken for regular monitoring.

Irregular red cell antibodies were sought by the indirect antiglobulin test, and enzyme and saline techniques at several temperatures using standard methods.[4] Direct antiglobulin testing was also done. Past cytomegalovirus infection was detected by the presence of antibodies using latex agglutination (CMV-Scan, Becton-Dickinson) and IgG ELISA (Captia CMV-G, Mercia Diagnostics). Epstein-Barr virus viral capsid antigen IgG antibodies were detected by immunofluorescence using P3 HR1 cells.[5] T cell subsets were measured in all patients by flow cytometry using a Coulter Electronics system. Serum β_2 microglobulin concentrations were measured by an ELISA (MELISA, Walker Diagnostics).

Results

Seven of the 11 children infected with HIV (64%) had cold agglutinins in the serum compared with one of nine (11%) in the control group. The cold agglutinins were of anti-I specificity in all children except one. The difference between these group is high significant χ^2= 6·455, 1 df, 95% confidence interval (CI).

All patients and controls had negative direct antiglobulin tests except for one child who was positive for HIV.

The presence of cold agglutinins in those patients who were positive for HIV did not correlate with mean T4 lymphocyte count, or serum β_2 microglobulin concentrations. Mean concentrations of immunoglobulins of all classes were increased in those children positive for HIV, but only for IgM was there a significant difference between the children positive for HIV who had cold agglutinins (mean IgM 2·1 g/l) and those who did not (mean IgM 1·1 g/l, p=0·036).

The incidence of antibodies to cytomegalovirus (2/11) and Epstein-Barr virus (9/11) was not increased in patients with cold agglutinins compared with those without (1/9 with antibodies to cytomegalovirus, and 8/9 with antibodies to Epstein-Barr virus).

One child positive for HIV had cold agglutinins the specificity of which could not be determined, and he also had a positive direct antiglobulin test as a result of coating with the complement components C3 and C3d. This child did not differ from the rest of the children who were positive for HIV in respect of the other variables.

Discussion

HIV infection is accompanied by a variety of disturbances of immune function including polyclonal B cell activation with raised immunoglobulin concentrations[1] and autoimmune phenomena. Red cell antibodies have been reported, but only rarely with any apparent clinical effects.[3] Anaemia is common in

Royal Liverpool Children's Hospital, Alder Hey, Liverpool
P H B Bolton-Maggs
L M Ball

Mersey Regional Blood Transfusion Centre, Liverpool
P D Rogan
J K M Duguid

Public Health Laboratory, Fazakerley Hospital, Liverpool
K J Mutton

Correspondence to:
Dr P H B Bolton-Maggs,
Department of Haematology,
Royal Liverpool Hospital,
Prescot Street,
Liverpool L7 8XP.

Accepted 16 January 1991

(*ArchDisChild* 1991;66:732–733).

HIV infection, but immune haemolysis is not a significant cause. In this group of children positive for HIV we found a significant incidence of cold agglutinins of anti-I specificity compared with a group of HIV antibody negative haemophiliac children. Cold agglutinins are usually of IgM class, and this is consistent with our finding of raised IgM concentrations in the children with cold agglutinins. Cold agglutinins have been described in adult homosexual patients positive for HIV,[2 6] and most commonly in those with symptoms related to the HIV infection. We found no association, however, between cold agglutinins and symptoms related to HIV infection.

Infective agents can cause sensitisation to red cells; both Epstein-Barr virus and cytomegalovirus infection are associated with the development of cold agglutinins. There were no differences between the two groups of patients in the incidence of seropositivity for cytomegalovirus or Epstein-Barr virus. It is likely therefore that the cold agglutinins in our patients were associated with the HIV infection itself.

Though six of our seven patients with cold agglutinins had anti-I, the other was unique in having cold agglutinins of undetermined specificity. He also had a positive direct antiglobulin as a result of coating with complement components, and he is transfusion dependent. His anaemia has only developed since starting therapy with azidothymidine, however, and does not seem to be caused by haemolysis as he has no reticulocytosis nor increase in his serum bilirubin concentration.

A single case of haemolytic anaemia associated with HIV infection which was associated with cold agglutinins has been reported and, unusually for cold antibodies, the patient responded well to treatment with steroids.[3] None of our patients had symptoms related to the cold agglutinins but we had difficulty in cross matching until the antibodies had been identified, which led to delay in providing compatible blood. Transfusions have been uneventful since then.

We can find no other reports of cold agglutinins in children with HIV infection. This group differs from previously described adult patients in that they have a high incidence of anti-I.

1 Falloon J, Eddy J, Wiener L, Pizzo PA. Human immunodeficiency virus infection in children. *J Pediatr* 1989;**114:** 1–30.

2 McGinniss MH, Macher AM, Rook AH, Alter HJ. Red cell autoantibodies in patients with acquired immune deficiency syndrome. *Transfusion* 1986;**26:**405–9.

3 Puppo F, Torresin A, Lotti G, Balleari E, Orlando G, Indiveri F. Autoimmune hemolytic anemia and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1988;**109:**249–50.

4 Petz LD, Garratty G. The serologic investigation of autoimmune hemolytic anemia. *Acquired immune hemolytic anemias.* London: Churchill Livingstone, 1980:139–84.

5 Lennette EH, Schmidt NJ. *Diagnostic procedures for viral, rickettsial and chlamydial infections.* 5th Ed. Washington: American Public Health Association, 1979:453–9.

6 Pruzanski W, Roelcke D, Donnelly E, Lui L-C. Persistent cold agglutinins in AIDS and related disorders. *Acta Haematol* 1986;**75:**171–3.

Archives of Disease in Childhood 1991; **66:** 734–736

CURRENT PROBLEM

Day case treatment for children

Harvey Marcovitch

Horton General Hospital,
Banbury OX16 9AL

Correspondence to:
Dr Marcovitch.

Treating children as day cases has been a familiar task for paediatricians[1] and most surgeons[2] for more than two decades. Born of a mixture of humanitarianism and expediency, day care is now encouraged by the Department of Health because of its perceived value for money.[3] Unfortunately, it is not invariably good value for child and parent, particularly as services have developed piecemeal and frequently depend more on the enthusiasm and energy of particular people than on any formal management plan.

Caring for Children in the Health Services (CCHS),* a working group that includes purchasers, providers, and consumers, has published its fourth report; this deals with day care and is entitled *Just for the Day*.[4] Numerous people and organisations were invited to give evidence, including Royal Colleges, professional and voluntary organisations, health authorities, hospitals, and parents. The findings are best introduced by the words of a consumer:

> 'A 3 year old was booked in as a day case for circumcision. The only preparation he or his parents received was a map of the hospital, an out of date guide to the children's ward (obviously designed for long stay inpatients), and instructions on overnight fasting. On arrival he was put to bed in a general paediatric surgical ward where the staff seemed to his mother to be far too busy with ill children to give him much of their time; nobody could predict when he would be going to theatre and his mother was not permitted to carry him or wheel him there, or to accompany him into the anaesthetic room. He was frightened by being transported on an adult sized trolley by two figures in theatre dress.
>
> By the time of operation he had been starved for 14 hours and had been pleading incessantly for a drink. Left at the theatre door his mother was not told where she might wait, when her son would be returned to the ward, or whether she could obtain refreshments for herself. Like many mothers she had starved vicariously with her child.
>
> He seemed comfortable when he returned but later attempts by his mother to obtain analgesia were met with the comment that nothing had been written up and the doctors were all in theatre. At 9 pm a nurse approached, seemed surprised to see them and said: "What are you doing here? You should have gone home hours ago" '.

The hospital concerned is a major teaching unit but complaints of this sort came from parents who had been dealt with in various hospitals which had in common only the lack of any coherent planning for day services.

The CCHS survey was not designed to report on current practice but the enormous bulk of information that was received allowed a reasonable assessment of what is happening. There are hospitals where the anecdote described above would be a most unlikely occurrence. In general these hospitals contain day units that were initiated and are sustained by enthusiasts with a designated director, often a nurse, acting within clear management policies.

In many hospitals, however, there are no special day case facilities for children, who are cared for together with adults without regard for their individual needs; day patients and inpatients are inappropriately mixed, clerical staff are few, and child day patients are rarely separately monitored and audited. Perhaps because of this there is often little thought given to these children as a discrete group: inadequate information for parents, non-existent operational policies, and too frequent admission overnight are some of the results.

Just for the Day aims to provide a managerial tool for hospitals to enable them to provide a quality of care equal to the best day units.[4] The result is a comprehensive set of standards, including principles for preadmission, transfer of care, and care in the community after discharge.

Day case investigation and treatment are an integral part of the philosophy that demands that separation of child from home and family should be kept to a minimum, that parents take part in decision making, and that they are made welcome in our hospitals. Despite the reluctance of some to change their style of practice the increasing proportion of day case treatment is evident. The Royal College of Surgeons of England has published guidelines to encourage surgeons and health authorities and trusts to undertake more day surgery.[5]

The CCHS has found that the increase in the amount of day surgery is much more apparent in adults than children; the report does not speculate on the reasons but one might easily be the greater pressure on adult inpatient beds as a result of financial squeeze. Of the district general hospitals offering evidence, one undertook 80% of its waiting list admissions as day cases and there is well documented information that more than half of all the general surgery of childhood can be carried out safely in this way.[6]

---

*Caring for children in the health services, 7 Belgrave Place, Clifton, Bristol BS8 3DD, represents: the Royal College of Nursing, the National Association of Health Authorities and Trusts, the National Association for the Welfare of Children in Hospital, and the British Paediatric Association. Co-opted were the British Association of Paediatric Surgeons, the Association of Anaesthetists of Great Britain and Ireland, and the College of Anaesthetists.

Yet, in many health districts, the figure is below 10%. An Audit Commission survey of 54 districts found that the day cases were 29·3% of hernia repairs, 17·4% of circumcisions, 55·4% of myringotomies, and 2·7% of squint corrections.[4]

It is too early to predict the effect on day surgery of the recommendations of the National Confidential Enquiry into Perioperative Deaths (NCEPOD), but one of them was that surgeons and anaesthetists should not undertake occasional paediatric practice and that consultants who care for children must keep up to date and competent in their management.[7] In district hospitals without paediatric surgeons this might usefully lead to an agreement whereby a particular surgical and anaesthetic team took major responsibility for operating on children. CCHS welcomed the setting up in 1990 of the British Association of Day Surgery the aim of which is to promote high standards throughout the United Kingdom.

So far as non-surgical day care is concerned, the national performance indicators for medical paediatrics show an average for day cases of only 2%, which tells us a lot more about the collection of data than it does about how paediatricians work.[8] The confusion between 'ward attenders' and day cases has been highlighted previously by the CCHS.[9] Many paediatric units are still careless over the keeping of these statistics, especially where resource management has made little impact. If the Department of Health is to have any inkling about the nature of paediatrics in hospitals it is vital that what goes on in children's wards is thoroughly documented and reported.

After assessing the information it received the CCHS recommended 12 quality standards for a planned package for day care that should be used in NHS contracts:

(i) The admission is planned in an integrated way to include preadmission, day of admission, and postadmission care, and to incorporate the concept of a planned transfer of care to primary or community services, or both.

(ii) The child and parent are offered preparation both before and during the day.

(iii) Specific written information is provided to ensure that parents understand their responsibilities throughout the episode.

(iv) The child is admitted to an area designated for day cases and not mixed with acutely ill inpatients.

(v) The child is neither admitted nor treated with adults.

(vi) The child is cared for by identified staff specifically designated to the day case area.

(vii) Medical, nursing, and all other staff are trained for and skilled in working with children and their families, in addition to having the expertise needed for day case work.

(viii) The organisation and delivery of patient care are planned specifically for day cases, so that every child is likely to be discharged within the day.

(ix) The building, equipment, and furnishings comply with safety standards for children.

(x) The environment is homely and includes areas for play and other activities designed for children and young people.

(xi) Essential documentation, including communication with the primary and community services, is completed before each child goes home so that aftercare and follow up consultations are not delayed.

(xii) Once care has been transferred to the home, nursing support is provided at a doctor's request by nurses trained in the care of sick children.

So that they can monitor providers' compliance with these standards, purchasers are enjoined by the CCHS to identify data from which children can be audited separately, day cases can be separated from inpatients, rates of transfer to inpatient care reviewed, children's and parents' opinions sought, and the effectiveness of integration of hospital and community services can be analysed.

Providers are also offered advice; for surgeons this is based on the Royal College of Surgeons of England's specially commissioned report, which has been updated by discussion with other professional bodies representing surgical and anaesthetic interests. It includes a list of procedures suitable to be done as day cases, and reminds clinicians of the American Society of Anesthesiology classification for patients requiring general anaesthetic. Special note is made of premature babies who are still only a few weeks past their full term age, or who have a history of ventilatory support.

There have been no similar published guidelines for medical paediatrics so the CCHS has taken evidence from all the subspecialties and devised a practical list. This includes tolerance tests, jejunal biopsy, endoscopy, imaging under anaesthesia, setting up or giving intravenous treatment, as well as multipurpose day admissions to undertake clinical measurements, investigations and discussion with parents and child—for example, in cystic fibrosis, cancer, or newly diagnosed diabetes mellitus.

Of course not all families can take advantage of day care facilities. A parent will usually need to stay throughout the day and will need to provide suitable transport, which certainly does not mean public transport, after the procedure. The adequacy of facilities at home need to be taken into account before booking a child as a day case.

A major problem, especially where there are entrenched views or where capital and space are in short supply, is where precisely to locate a children's service. In *Just for the Day* this is discussed, and various models are described as well as the ideal. It is best if children are kept together in a purpose designed day unit close to the operating theatres or with its own integral theatre and recovery facilities. An alternative, widely practised at present, is to base children on a general children's ward. This has disadvantages, which were made clear by many of the respondents to the CCHS inquiry; both staff and parents report the danger of day cases becoming 'second class' or 'lodgers' because they are not given a high priority compared with inpatients who may be more ill. There is unquestionably a greater chance of the admission continuing overnight when the unit is not specifically designed for day care.

Where management on the ward is unavoidable, a reasonable compromise would be to provide a separate area of the ward dedicated to day cases who are then nursed by designated staff without other duties. It might even be practical for it to double as overnight parental accommodation. Of course, if the ward is a long way from the operating theatres this may simply not be feasible.

An alternative might be to provide a children's day room for medical procedures (and perhaps endoscopy) both for day patients and ward attenders. Under these conditions surgical day care would be carried out on an adult or mixed day unit. This option will not appeal to paediatricians, paediatric nurses, and managers of children's services who are likely to feel that the environment, staffing, and facilities will not meet national recommendations.[10-12]

If such a system is unavoidable there may be ways around the problem: for example, an occasional or periodic children's list can be built up so that, for that particular session, the unit is used for children only. Successful adoption of this system was reported to the CCHS from Exeter and Winchester. At Kingston and Colchester small groups of children were admitted to a special room where they could be active preoperatively, and recover postoperatively, separately from adults in the unit.

Clinical directors must consider how day units should be staffed. Day cases pose a particular problem for junior medical staff who can be forgiven for seeing them as having a lower priority than some of their other patients, but the demands are great and time is short when dealing with such children and their families. These doctors deserve a formal, explicit statement of their duties in this respect. There should be distinct nursing staff; it is likely that there are a considerable number of registered sick children's nurses or others trained and experienced in the care of sick children who are not currently employed in the NHS but prepared to return to a flexible part time job. An administrator, who may be from a clerical or nursing background, is essential.

A day should be as short as possible. Vessey *et al* have pointed out that being asked to arrive too early provokes a period of great stress, with an irritable, hungry, and apprehensive child (and mother).[13] Stepped appointment times offer better quality of care but anaesthetists and surgeons have told the CCHS that with current staffing levels and intensive theatre use such a system may not be practicable. Despite this, issues must be discussed among surgeons, anaesthetists, and nurses so that the reasoning is clear to all. The sort of questions that arise are, for example: Would parents be willing and able to wake a child at 6 am for a drink to cut down starvation time? Would it be preferable to have children on an early afternoon list so that they can have breakfast? Should babies be at the beginning of the list to avoid dehydration or in the middle so that they can have an early morning feed?

Many units have provided leaflets and information sheets for parents and children. Some are well worth plagiarising—that from Southampton, for example. With the more complex consent forms now coming into use, documentation will take even longer. Surgeons who do not already do so might consider obtaining informed consent at the time of the outpatient visit that precedes the booking.

In *Just for the Day* evidence from a wide range of sources has been sifted through a group close to where the work is done. Because of this it deserves wide circulation; paediatricians and surgeons who wish to set up day case services or audit their current practice can do no better than to use it as a working document. The CCHS has produced a statement summing up the principles it sees as most important in developing policies. For those of us instructed to prepare a 'philosophy' or 'mission statement' it is readymade.

Most children, when they are sick are cared for by their families within their own homes, with the help of their general practitioners and community nurses. Children are more vulnerable emotionally than adults so should be admitted to hospital only if the care they require cannot be provided equally well at home, since hospitalisation can be a distressing and difficult experience.

An admission should always be child-centred, based on a partnership between the family and the health care team. Children should not be nursed alongside adults when hospital care is necessary and should not be admitted overnight if an equivalent level of care can be provided on a day basis. Such admissions involve parents in additional responsibilities and entail careful preparation and support of the family and effective communication between the hospital and primary/community support team.

The planning and delivery of care should recognise the multicultural nature and diverse needs of the population and provision should be made accordingly.

1 Marcovitch H, Davenport HT, Grant DB, Liberman MM, Valman HB. District paediatric day care. *Arch Dis Child* 1975;50:648–51.
2 Lawrie R. Operating on children as day cases. *Lancet* 1964;ii: 1289–91.
3 Department of Health. Discharge of patients from hospital. HC(89)5. London, HMSO, 1989.
4 Thornes R. *Just for the day: children admitted to hospital for day treatment*. Bristol: Caring for Children in the Health Services, 1991.
5 Royal College of Surgeons. Commission on the provision of surgical services. *Guidelines for day case surgery*. London: Royal College of Surgeons of England, 1988.
6 Atwell JD, Gow MA. Paediatric trained district nurse in the community: expensive luxury or necessity. *BMJ* 1985;291: 227–9.
7 Campling EA, Devlin HB, Lunn JN. *The report of the national confidential enquiry into perioperative deaths*. London: NCEPOD, 1990.
8 Department of Health. *Health services indicators dictionary*. London: HMSO, 1990.
9 Thornes R. *Hidden children: an analysis of ward attenders in children's wards*. Bristol: Caring for Children in the Health Services, 1988.
10 Report of the committee on the welfare of children in hospital. *The welfare of children in hospital*. London: HMSO, 1959. (Platt report.)
11 Department of Health and Social Security. *Hospital facilities for children*. HM(71)22. London: HMSO, 1971.
12 National Association for the Welfare of Children in Hospital. *Charter for children in hospital*. London: National Association for the Welfare of Children in Hospital, 1984.
13 Vessey JA, Caserza CL, Bogetz MS. In my opinion . . . another Pandora's box? Parental participation in anaesthetic induction. *Children's Health Care* 1990;19:116–8.

Archives of Disease in Childhood 1991; **66**: 737–741

CURRENT TOPIC

Childhood autism: its diagnosis, nature, and treatment

Sula Wolff

University Department of Psychiatry,
Royal Edinburgh Hospital,
Morningside Park,
Edinburgh EH10 5HF

Correspondence to:
Dr Wolff.

Leo Kanner,[1] although not the first to describe this serious and intriguing developmental disorder of early childhood,[2] so precisely captured its essential features that the clinical account of his first 11 cases has never been bettered. The salient characteristics he mentioned were an 'extreme autistic aloneness' from the beginning of life, delay and abnormality in language acquisition with echolalia and pronomial reversal, and 'an obsessional desire for the maintenance of sameness' in the presence of islets of normality, in particular an excellent rote memory. He saw the primary deficit as an inborn disturbance of affective contact and later described similar, although very mild features of emotional coldness and obsessionality in the parents.

Since then research into autism and related developmental disorders has flourished, there is a journal entirely devoted to them and, although they are so rare, their elucidation promises to shed light on many unanswered questions both about normal development of language and sociability and about the nature of a number of clinical conditions.

Recent growth areas of research have been the genetics of autism, the relation between autism and allied clinical syndromes, the nature of the psychological dysfunctions of autistic people, and the effects of specific treatment interventions. There have also been changes in how the condition is perceived and classified in the newer systems of diagnostic classification. Before reviewing recent progress, some basic facts must be recalled.

Age of onset, sex, social class incidence, prevalence, and prognosis

Though most cases, as Kanner himself noted, develop the disorder insidiously from birth, in some there is an early period of apparently normal social and language development followed by a set back. Autism is distinguished from other pervasive developmental disorders, as we shall see, by its onset before 30 to 36 months of age. More boys than girls are affected (a ratio of about 2·5–3:1). The sex ratio is more equal when autism is associated with organic brain disease or severe mental retardation. The social class distribution of families with autistic children has been found upwardly skewed in some studies, especially in well functioning autistic children,[3] but not in others.[4] A number of epidemiological prevalence studies have found two to four autistic children in every 10 000, more if severely retarded children with autistic features are included.[2]

There have been several long term follow up studies of autistic clinic attenders but only two of total population samples.[5 6] Gillberg and Steffenburg followed up 23 autistic children and 23 with 'other psychoses', often associated with organic handicapping conditions, to the age of 16–23 years.[6] In 17% of both groups outcome was 'good' or 'fair', and in 44% of autistic and 70% of other psychotic children it was 'poor' or 'very poor'. Among this still quite young group of subjects only one was self supporting, 23 lived with parents, 20 in institutions for the handicapped, and one in a psychiatric clinic. Altogether 35% of the total group (29% of autistics) had developed epilepsy, 50% between 13 and 14 years. One half had deteriorated symtomatically in early adolescence with no difference between the two groups. A perceptive observation was that, while as children the autistics were often particularly attractive to look at, after puberty their appearance tended to coarsen, often becoming clearly deviant. As in previous studies, the best predictors of outcome were a preschool measured intelligence quotient (IQ) of 50 or more and the presence of communicative speech before the age of 6. Epilepsy and fragile X chromosome abnormality were associated with a worse outcome.

Although many early symptoms—echolalia, social withdrawal, and stereotypies—tend to disappear with age, severe social impairments and abnormalities of language use remain, and the overall outlook for autistic children is poor. Nevertheless, that minority whose intelligence is within the normal range can do surprisingly well despite serious childhood abnormalities. Szatmari *et al* found that among 16 autistic children with mean IQ of 92, four had 'recovered' at a mean age of 26 years, living independent lives and with long term relationships.[7] One had married. Eight in all were totally independent, six needed only minimal supervision, and seven had obtained university degrees. On the other hand, even among these rare well functioning autistics, one was profoundly retarded at follow up, one had chronic schizophrenia, three had hallucinations, and two paranoid thinking. Two were unemployed, three in sheltered workshops, and nine had never dated.

Diagnostic classification, diagnostic instruments, diagnostic criteria

The diagnostic criteria for autism have changed in emphasis over time[8] as the condition has come to be viewed not so much as a psychosis specific to childhood, as in the *International Classification of Diseases*, 9th revision (ICD-9),[9] but rather as a deviation of multiple developmental processes. This gave rise to the DSM-III (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition) and DSM-III-R (revised edition) concept of 'pervasive developmental disorder'[10 11] and contributed to the envisaged changes for ICD-10.[12] Here too autism is classified as a pervasive developmental disorder. This concept, like that of the specific developmental disorders,[12] involves an onset very early in life, impairment of functions related to biological maturation, a steady course without appreciable remissions and relapses, improvement with age, an increased incidence in males, and an often familial association with similar or related disorders. This concept has justly been criticised as not in itself logical nor fully applicable to childhood autism[13] (autism does not affect all developmental areas, its course is not always steady from birth and, while symptoms change over time, only a few cases improve with maturation). The diagnostic criteria for autism itself, however, are clear and there is good evidence for their validity.[8] A detailed autism diagnostic observation schedule and an autism diagnostic interview of excellent reliability and validity, have recently been developed for research purposes by an international research group.[14 15]

The diagnosis of autistic disorders, as they are now called, rests on three main groups of symptoms:

(1) Qualitative impairment and deviance of reciprocal social relationships with abnormalities of gaze and social responsiveness to other people, especially other children.

(2) Deviant development of language and other communication skills, with either no language at all, early onset followed by loss of speech, or delayed onset and characteristic language features such as immediate and delayed echolalia, pronomial reversal, metaphorical expressions and, especially, a failure in language use (in the 'pragmatics' of language), relative to available comprehension and language skills.

(3) Repetitive, stereotyped patterns of behaviour, which include Kanner's 'obsessive desire for the maintenance of sameness', but also prolonged attachments to particular objects, the formation of rows of toys irrespective of the needs of the rest of the household, extreme food fads, repetitive questioning often with insistence on ritualistic 'to and fros' with others, and motor stereotypies.

While age of onset distinguishes well between autistic disorders and early onset schizophrenia, which rarely begins before puberty, childhood disintegrative disorders as they are to be called in ICD-10 (the former disintegrative psychoses) tend to manifest only after the age of 3 and autism usually before 30 months. In this classification age of onset, the fourth criterion, has been set to under 3 years to improve differentiation from disintegrative disorders with their much poorer prognosis (DSM-III-R, still uses the 30 months cut off between early and 'late onset' autism).

Differential diagnosis: the borderlands of autism

Half of severely retarded children (IQ less than 50) have symptoms of autism.[16] Although their educational and treatment needs resemble those of autistic children and they need much one to one teaching to compensate for their social unresponsiveness, for research purposes a clear distinction must be made. For research and practice it is also important to differentiate autistic children from those rare cases of disintegrative disorder after a period of at least three years of apparently normal development. While the aetiology of this condition generally remains unknown, it may be caused by progressive, degenerative brain disease such as cerebral lipoidosis or leucodystrophy. The end state is usually one of severe mental handicap with no available language. Rett's syndrome may be symptomatically indistinguishable from autism because of its early onset, but occurs predominantly in girls and is associated with normal prenatal and perinatal development. Rett's syndrome is also distinguishable by a decrease in head growth after 5 months of age, loss of hand skills between 6 and 30 months, and increasing gait and trunk apraxia and ataxia.[17] Doubt has recently been cast on the assumption that the fragile X chromosome abnormality, perhaps the second most common cause of mental retardation, is also specifically linked to autism. Payton *et al* found a 2·4% incidence of this abnormality in 85 autistic males, similar to that in a mentally retarded male population.[18]

The differential diagnosis of autism from schizophrenia, specific developmental language disorders, and Asperger's syndrome (also referred to as schizoid or schizotypal personality disorder) is less problematical in clinical practice, but raises many aetiological issues to be discussed next.

Aetiology

Goodman has clearly summarised the arguments in favour of multiple coexisting factors in the causation of autism, although he does not make the point that the condition may be so rare because it requires the coincidence of more than one, perhaps quite common, causal agents.[19] Goodman focuses especially on the coexistence of distinct constellations of functional impairments necessary for autism: impairments of general intelligence, deficits in mechanical language skills, as in the developmental dysphasias, and deficits in social relatedness, play and non-verbal communication as in Asperger's syndrome. A difficulty here is that a number of children with specific developmental language disorders also have social deficits resembling those of Asperger/schizoid/schizotypal disorders,[20] and almost half the boys with these disorders had serious or multiple specific developmental delays of language related skills (S Wolff, unpublished observations).

Two types of causal agents have been identified: those associated with brain damage and genetic factors. It is known that autistic children have somewhat higher rates of paranatal abnormalities and that they are prone to develop epilepsy, not so much in infancy and early childhood as are mentally retarded and severely birth injured children, but in early adolescence. In a minority of cases there is a specific association with some types of cerebral disorder and not with others (with congenital rubella and tuberous sclerosis for example, but not with Down's syndrome or cerebral palsy).[2] Moreover, when monozygotic twins are discordant for autism, it is the autistic twin who more often had evidence of paranatal injury.

There have been three population based twin studies of autism: two in the UK, including a follow up of one set of twins into adult life, and one in Scandinavia (A LeCouteur, *et al*; paper presented at First World Congress on Psychiatric Genetics, Cambridge, 1989).[21, 22] The concordance rate for autism itself in monozygotic pairs ranged from 36 to 91% and in dizygotic pairs from 0 to 10%. The concordance rates for other cognitive and social impairments, including global and specific developmental delays and deficient or unusual social responsiveness (which tended to get worse with age), ranged from 82 to 91% in monozygotic pairs and from 0 to 30% in dizygotic pairs. Clearly, what is inherited is either the full syndrome or a lesser variant consisting of both cognitive and social impairments.

Further evidence for this comes from the studies of siblings and other biological relatives of autistic children. The evidence, still requiring confirmation, is of an excess of cognitive delays among the siblings of severely retarded autistic children, and an excess of minor social impairments of the Asperger/schizoid/schizotypal kind in the parents and other biological relatives of high functioning autistics.[23, 24] Piven *et al* found an excess of autism (3%), of 'severe social dysfunction and isolation' (4·4%), and of cognitive disorders (15%) in adult siblings of autistic children, especially in those who had been diagnosed by Kanner himself.[25]

There is no excess of schizophrenia in the biological relatives of autistics and no excess of the much rarer condition of autism in the relatives of schizophrenics. The two conditions are clinically distinct in their symptomatology, age of onset, sex, and social class distributions and associations with mental retardation and epilepsy.[26] They may nevertheless share a genetic predisposition to the schizophrenia spectrum disorders of the Asperger/schizoid/schizotypal kind. Altogether 75% of children diagnosed 'schizoid' have the features of schizotypal personality disorder in adult life and this is firmly part of the schizophrenia spectrum (S Wolff *et al*, unpublished observations). The symptoms of such children: solitariness, lack of empathy, the single minded pursuit of special interest patterns, unusual modes of communication, and oversensitivity, although different, resemble those of autism in that they are all features of deficits in social and emotional relationships with other people and in communication skills, together with single minded pursuits of particular interests or behaviours. There have also been a few case reports of families with both an autistic child and a child with Asperger's syndrome, and series of cases have been reported in which a very early onset of schizophrenia was preceded by a clear cut autistic syndrome.[27]

Autism is likely to be a heterogeneous condition, with different causal factors operating in different groups of cases.[21] In a very few the clinical syndrome is associated with chromosomal or single gene abnormalities: fragile X chromosome, phenylketonuria, tuberous sclerosis, or neurofibromatosis; in others with infections: congenital rubella; and in yet others with evidence of diffuse brain dysfunction. Although symptomatically similar, severely mentally handicapped and well functioning autistic people may differ in the causal agents and pathologies involved. The genetic basis too may differ in different groups of cases and may involve single or multiple genes.

So far, while brain lesions have increasingly been found with the newer technologies in autistic children, no consistent pattern has emerged and children with and without such lesions do not differ symptomatically.[28] No specific metabolic abnormalities have been identified. High serotonin concentrations have been found in one third of autistic children, but also in severely retarded non-autistic children,[29] and the results of treatment with fenfluramine to counteract such high concentrations have been equivocal.

The nature of the deficits

The early work of Hermelin and O'Connor, in which psychological functioning of autistics was compared with that of IQ matched retarded and normal children, showed impaired encoding and restructuring of information.[30] Although short term memory, for example for random words, was normal, the memory of autistics unlike that of controls did not improve for word sequences with meaning. Autistic children could not use redundancy to improve their memory span. Moreover, their language deficit was but one aspect of a more general inability to use signs and symbols, and they were better at processing spatial than temporal sequences; this is in line with their often remarkable jigsaw solving skills.

Since then there have been a number of imaginative explorations of the autistic child's specific functional disabilities. Peter Hobson, again comparing autistic with normal and mentally retarded subjects, examined their capacity to match videos of people's vocalisation, facial expression, and activities associated with those emotions that have clear cut facial expressions (anger, fear, happiness, and sadness) against photographs and line drawings of faces or activities expressing these same emotions.[31] He found autistics specifically impaired in the recognition of vocalisations and facial expressions of emotions. Even as adults autistic people are deficient both in the recognition and expression of emotions verbally (that is, in their tone of voice) and facially.[32] Hobson believes that the basic flaw in autism is in the biologically based capacity, normally present in everyone, for attention and empathic responsiveness to the emotional expression and emotional behaviour of others.

Simon Baron-Cohen[33] and Uta Frith[34] see these difficulties as part of a more general cognitive deficit: an impairment in the capacity to infer what is in the minds of others—that is, a lack of a 'theory of mind'. In one of a series of imaginative experiments autistic, Down's syndrome, and normal children were shown two dolls, one with a basket and one with a box. The first doll puts some marbles in her basket and goes out. The second then takes the marbles from the basket and puts them in her box. The first doll returns, and the question to the experimental child is: where does the first doll look for the marbles? The autistic children tend to answer: in the box, because that is where they known the marbles to be. Other children of similar IQ can put themselves into the 'mind' of doll number one, know that this doll is unaware of the transfer of marbles, and correctly point to the basket as the container first to be explored. Frith sees autistic individuals as 'natural behaviourists', who do not feel the normal compulsion to weave together mind and behaviour for the sake of coherence.

Baron-Cohen believes the primary defect in autism to be cognitive; Hobson sees it as primarily emotional. Yet both sociability and prelinguistic behaviour develop together towards the end of the first year of life and, though linguistic-cognitive and emotional abilities are often selectively impaired (for example, in the retarded or in children with specific developmental delays), there is no reason why these two types of functions, so intimately connected in the development of the baby, should not be impaired together. Frith makes clear that the specific autistic impairments, which include also the absence of make believe play, of role modelling, and an inability to distinguish pretence play from reality, all involve competencies which normally begin to develop in the second year of life. This is also the time at which correct empathic responses to distress in others are first seen and is precisely the time at which the symptoms of autism first become apparent. Although the basic defect is likely to be inborn, it does not manifest until the time at which the impaired functions normally appear.

Treatment approaches

There have been two excellent controlled studies of treatment interventions for autistic children, one now a classic,[35 36] the other more recent.[37] The first demonstrated clearly the superiority of a structured, behaviourally oriented teaching approach geared to the child's particular developmental level, and with much one to one teaching and contingent reinforcements. The children progressed more both educationally and socially, with less repetitive stereotyped behaviour in free play settings, than children at schools where a permissive approach was emphasised and the focus was on responding to possible underlying emotional problems. Even with the most effective methods, however, no child with an IQ below 50 gained useful skills in literacy or numeracy.

The more recent study by Howlin and Rutter of the efficacy of an intensive, home based, behaviourally oriented intervention has been reported in a book that has much to teach all clinicians who look after autistic children, because it focuses also on the problems of parents and the other children in affected families.[37] It makes clear that, whatever the specific technical interventions, families with an autistic child are coping with particularly stressful circumstances and require skilled counselling in their own right. Such families need informed recommendations for special schooling for the child, and social work services providing access to facilities for respite care, holidays, financial entitlements, and special, often residential, settings for the autistic person at and after adolescence. Due emphasis is given to the practical help and emotional support that can come from joining the National Autistic Society or one of its local equivalent organisations.

As for the specific treatment interventions, they were individually tailored to the needs of each autistic child and family, with highly specific treatment goals. The focus was on fostering the development of language, play, and social interactions. Treatment also aimed to decrease the specific obsessional, ritualistic behaviour of the autistic children, and to help parents reduce their children's often so distressing general behavioural difficulties such as sleep and elimination disorders, food fads, temper tantrums, and screaming attacks. Parents were the therapists, but care was taken not to impose too time consuming a programme on them. While behavioural techniques of operant learning with prompting, fading, reinforcement procedures and 'time out', if necessary, were taught to the mothers by demonstration in their homes after a full functional analysis of the child's behaviour, the approach to the families as a whole used psychotherapeutic methods also.

In this study treated children (all with an IQ of 60 or more and without associated medical conditions) were compared with matched control groups both for short term gains (at six months) and for long term outcome (at 18 months). In the short term, the greatest improvement was in reducing the children's general disruptive behaviour and their ritualistic and other solitary activities. The overall level of language usage also improved significantly, with reduction of echolalia and stereotyped utterances, but there was little difference in the level of language complexity between treated and control groups, both of which improved over time. Mothers of children just on the threshold of speech were best able to put what they were taught into practice, presumably because their children were the most rewarding to teach. In the long term, treatment worked best for general disorders such as temper tantrums, aggression, sleep and toiletting difficulties; it also reduced but never totally removed specific autistic rituals and routines. Play and social behaviour was also improved relative to the controls but always remained severely restricted. The communicative use of language, but not language competence, improved also, but there was no difference at all in the overall level of cognitive capacity. The authors caution that all treatment approaches need to be so structured that the demands on the parents are reduced rather than increased, but also that, to avoid disppointment and frustration, treatment goals must be realistic. The results of this well controlled study will certainly contribute to this. The study also demonstrates that without adequate controls new treatments can all too easily engender false hopes.

There has recently been much publicity for 'holding therapy'. While this emotionally exhausting method may well lead to some increase in emotional contact between the autistic child and the 'holding' parents immediately after the session, there have been no properly controlled outcome studies to back up the often extravagant claims for the efficacy of this method.

What is clear, in the management of autistic children and their families, is first the need for all affected children to be diagnosed and for possible associated neurological or genetic abnormalities to be identified. Whether or not such pathologies exist, all autistic children should be notified to the educational services so that they can benefit from the special educational arrangements they need and which are increasingly available in the UK as a result of local authority endeavours and the resources established by the parent societies for autistic children. Second, all families with autistic children need long term care and support to ensure their access to all the treatment and back up services they may need as the child grows up. These include intensive, home based specific behavioural treatment approaches as outlined by Howlin and Rutter for those children likely to respond[37]; short term medication with major tranquillisers to cope with particularly distressing episodes of behaviour problems; and an understanding of the possible personality and marital difficulties of the parents and of the stresses on the siblings of the autistic child with appropriate support and counselling. It is also important to have social work help to ensure the families have access to their financial entitlements and to holiday and other respite services and more intensive back up at adolescence when many autistic children will require day or residential units designed for their particular needs. Autistic children cannot generally benefit from work training centres set up for non-autistic handicapped young people. The National Autistic Society and other locally based parent societies for autistic people have contributed much in the setting up of special schools and adult units and in offering mutual support services for parents.

1 Kanner L. Autistic disturbances of affective contact. *The Nervous Child* 1943;2:217–50.
2 Rutter M. Infantile autism and other pervasive developmental disorders. In: Rutter M, Hersov L, eds. *Child and adolescent psychiatry: modern approaches.* Oxford: Blackwell 1985:545–66.
3 Lotter V. Epidemiology of autistic conditions in young children II: some characteristics of the parents and children. *Soc Psychiatry* 1967;1:163–73.
4 Gillberg C, Schauman H. Social class and autism: total population aspects. *J Autism Dev Disord* 1982;12:223–8.
5 Lotter V. Social adjustment and placement of autistic children in Middlesex: a follow-up study. *Journal of Autism and Childhood Schizophrenia* 1974;4:11–32.
6 Gillberg C, Steffenburg S. Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord* 1987;17:273–87.
7 Szatmari P, Bartolucci G, Bremner R, Bond S, Rich S. A follow-up study of high-functioning autistic children. *J Autism Dev Disord* 1989;19:213–25.
8 Rutter M, Schopler E. Autism and pervasive developmental disorders: concepts and diagnostic issues. *J Autism Dev Disord* 1987;17:159–86.
9 World Health Organisation. *International classification of diseases.* 9th Revision. Geneva: WHO, 1978.
10 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III).* 3rd Ed. Washington, DC: American Psychiatric Association. 1980.
11 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III-R).* 3rd Ed revised. Washington, DC: American Psychiatric Association, 1987.
12 Rutter M. Child psychiatric disorders in ICD-10. *J Child Psychol Psychiatry* 1989;30:499–513.
13 Gillberg C. Autism and pervasive developmental disorders. Annual Research Review. *J Child Psychol Psychiatry* 1990; 31:99–120.
14 LeCouteur A, Rutter M, Lord C, *et al.* Autism diagnostic interview: a standardized investigator-based instrument. *J Autism Dev Disord* 1989;19:363–87.
15 Lord C, Rutter M, Goode S, *et al.* Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord* 1989;19:185–212.
16 Wing L. Language, social and cognitive impairments in autism and severe mental retardation. *J Autism Dev Disord* 1981;11:31–44.
17 Gillberg C. The borderland of autism and Rett syndrome: 5 case histories to highlight diagnostic difficulties. *J Autism Dev Disord* 1989;19:545–59.
18 Payton JB, Steele MW, Wenger SL, Minshaw NJ. The fragile X male and autism in perspective. *J Am Acad Child Adolesc Psychiatry* 1989;28:417–21.
19 Goodman R. Infantile autism: a syndrome of multiple primary deficits. *J Autism Dev Disord* 1989;19:409–24.
20 Cantwell DP, Baker L, Rutter M, Mahood L. Infantile autism and developmental receptive dysphasia: a comparative follow-up into middle childhood. *J Autism Dev Disord* 1989;19:19–31.
21 Folstein S, Rutter M. Autism: familial aggregation and genetic implications. *J Autism Dev Disord* 1988;18:3–30.
22 Steffenburg S, Gillberg C, Hellgren L, *et al.* A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry* 1989;30:405–16.
23 Wolff S, Narayan S, Moyes B. Personality characteristics of parents of autistic children: a controlled study. *J Child Psychol Psychiatry* 1988;29:143–53.
24 Narayan S, Moyes B, Wolff S. Family characteristics of autistic children: a further report. *J Autism Dev Disord* 1990;20: 523–35.
25 Piven J, Gayle J, Chase GA, *et al.* A family history study of neuropsychiatric disorders in the adult siblings of autistic individuals. *J Am Acad Child Adolesc Psychiatry* 1989;29: 177–83.
26 Kolvin I. Psychoses in childhood—a comparative study. In: Rutter M, ed. *Infantile autism: concepts, characteristics and treatment,* London: Churchill Livingstone, 1971:7–26.
27 Watkins JM, Asarnow RF, Tanguay PE. Symptom development in childhood onset schizophrenia. *J Child Psychol Psychiatry* 1988;29:865–78.
28 DeLong GR, Bauman ML. Brain lesions in autism. In: Schopler E, Mesibov GB, eds. *Neurobiological issues in autism.* New York: Plenum, 1987:229–42.
29 LeCouteur A, Trygstad O, Evered C, Gillberg C, Rutter M. Infantile autism and urinary excretion of peptides and protein-associated peptide complexes. *J Autism Dev Disord* 1988;18:181–90.
30 Hermelin B, O'Connor N. *Psychological experiments with autistic children.* London: Pergamon, 1970.
31 Hobson RP. Beyond cognition: a theory of autism. In: Dawson G, ed. *Autism: nature, diagnosis, and treatment.* New York: Guilford, 1989:22–48.
32 Macdonald H, Rutter M, Howlin P, *et al.* Recognition and expression of emotional cues by autistic and normal adults. *J Child Psychol Psychiatry* 1989;30:865–77.
33 Baron-Cohen S. Social and pragmatic deficits in autism: cognitive or affective? *J Autism Dev Disord* 1988;18: 379–402.
34 Frith U. *Autism: explaining the enigma.* Oxford: Blackwell, 1989.
35 Bartak L, Rutter M. Special educational treatment of autistic children: a controlled study. I: Design of study and characteristics of units. *J Child Psychol Psychiatry* 1973;14: 161–79.
36 Rutter M, Bartak L. Special educational treatment of autistic children: a controlled study. II: Follow-up findings and implications for services. *J Child Psychol Psychiatry* 1973; 14:241–70.
37 Howlin P, Rutter M. *Treatment of autistic children.* London: Wiley, 1987.

Archives of Disease in Childhood 1991; 66: 742–744

REGULAR REVIEW

Chronic inflammatory bowel disease

I W Booth

University of Birmingham, Institute of Child Health, Francis Road, Birmingham B16 8ET

Correspondence to: Dr Booth.

To be consigned to a life spent searching for the aetiology of inflammatory bowel disease remains as much a cause for supplication to St Jude as it ever did. Over the last decade new forms of inflammatory bowel disease have been described, the surgical management of ulcerative colitis has seen the impact of restorative proctocolectomy, and major changes have taken place in the medical management of Crohn's disease in childhood and adolescence. It is therefore appropriate to review some of these developments.

Epidemiology

The rapid increase in the incidence of Crohn's disease that took place in all age groups from the mid-1950s (0–2, increasing to 5–6 per 100 000 per year) may now have levelled off, although results in this respect are conflicting.[1] In contrast, the incidence of ulcerative colitis has remained virtually unchanged and still varies between five and 10 per 100 000 per year.

No single dietary factor has been unequivocally implicated in the pathogenesis of the classical forms of inflammatory bowel disease, but it is of interest that further evidence has appeared which suggests that lack of breast feeding, and episodes of diarrhoeal disease during infancy, predispose to the development of childhood Crohn's disease.[2]

Crohn's disease

PRESENTATION AND DIAGNOSIS

Anorexia nervosa

The need to consider carefully the diagnosis of Crohn's disease in adolescents with apparent anorexia nervosa is well recognised, but mistaken diagnoses continue.[3] There are almost always sufficient symptoms, signs, or abnormal laboratory results to suggest underlying organic disease and the abnormal ideation relating to body image is absent.

Panenteric disease

Crohn's disease has long been recognised as affecting potentially the entire gut, but the frequency of proximal gastrointestinal involvement in childhood has been recognised only recently. Thirty per cent of affected children and adolescents in a large Canadian series,[4] and 42% in a French series,[5] had evidence of Crohn's disease on upper gastrointestinal endoscopy.

Multiple aphthous ulcers in the oesophagus, gastric antral rigidity, granularity, linear ulceration and irregular thickening of the folds or cobblestoning in the duodenum were the commonest lesions. Upper gastrointestinal endoscopy may therefore be helpful in evaluating patients with suspected Crohn's disease in whom histological evidence is lacking and in patients with so called indeterminate colitis.

Growth failure and sexual immaturity

Up to a third of patients experience growth failure, usually with associated delayed skeletal maturation and sexual immaturity. The corresponding figure for ulcerative colitis is probably between 5 and 10%. The definition of growth failure varies, but must be a dynamic one, and a reduction in height centile of more than 0·3 SDs per year, a growth velocity of less than 5 cm per year, or a decrease in height velocity of at least 2 cm from the previous year during early to mid-puberty are all reasonable.[6] Bone age is usually at least two years behind chronological age.

A recent study from Scotland, where three quarters of children with inflammatory bowel disease were in the hands of physicians or surgeons, provides a strong argument for such patients being cared for by paediatric gastroenterologists.[7] In contrast to paediatricians, who invariably recorded height, physicians and surgeons rarely did so. Growth failure often went unrecognised and therefore untreated.

Atypical Crohn's disease

In addition to panenteric involvement, Crohn's disease may also involve structures remote from the gut. Recent reports of pulmonary and cutaneous granulomatous reactions in children with Crohn's disease emphasise the potentially multisystem nature of the disorder.[8]

Orofacial granulomatosis is a term used to describe the characteristic constellation of enlargement of the lips, diffuse facial swelling, gingival hyperplasia, oral ulceration, and buccal mucosal tags, which on biopsy are shown to contain non-caseating granulomata. It is becoming clear that up to a one third of such patients have evidence of more widespread involvement of the gastrointestinal tract,[9] and the term oral

Crohn's disease is therefore probably preferable.[10]

NUTRITIONAL TREATMENT

Induction of remission

An elemental, chemically defined diet, with exclusion of all other foods for six weeks is now recognised to be at least as effective as steroids in inducing remission of active disease.[11] Diet induced remission occurred in over 80% of a recent retrospective series, irrespective of the site of the disease, and remission was at least as long as when steroids were used (22% relapsed within six months, and 8–10% each subsequent year.[12] There is an additional benefit for children and adolescents in that linear growth six months after treatment with an elemental diet is substantially better than in those patients given steroids.[13]

The precise mechanism of the beneficial effect of elemental diets is uncertain, but the observation that successful induction occurs twice as commonly with an elemental, amino acid based feed (75%), as with a polymeric feed (36%), suggests that exclusion of intact protein from the gut is an important factor.[14]

Reversal of growth failure

Growth failure in Crohn's disease is sensitive to both enteral or parenteral nutrition, an outcome which is consistent with the notion that long standing undernutrition is important in the pathogenesis.[15] Overall, studies of nutritional repletion have shown that it is possible to convert a low initial height velocity of between 0·5–0·9 cm per six months to between 3·0–4·5 cm per six months after intervention.

Two recent publications are of interest, each of which has used nutritional supplementation to address the problem of growth failure in prepubertal patients. One used an intermittently administered elemental diet given by overnight nasogastric feeding for one month in four. This resulted in significant increases in growth velocities and reductions in both prednisolone intake and disease activity scores.[16] The second study used an overnight nasogastric supplement to increase energy intake in growth retarded adolescents by between 4·18 and 6·27 MJ (1000 and 1500 kcal) per day. The formula was non-elemental and, in contrast to the previous study, patients were encouraged to eat normally. In non-treated controls, height velocity remained unchanged, whereas in supplemented patients substantial improvements occurred in both height and weight during the year (6·98 cm and 11·75 kg respectively).[17]

Although there is convincing evidence to support energetic nutritional treatment in the management of growth failure, it is also important not to overlook the role of surgery. Two recent publications support early surgical intervention in adolescents with growth failure due to resectable disease. In addition to relieving symptoms, each study demonstrated an improvement in growth after surgery.[18 19] In one study nearly three quarters of operated patients had at least a doubling of preoperative growth velocity.[19]

Ulcerative colitis

EXTENSION OF PROCTOSIGMOIDITIS

Proctosigmoiditis is fairly common in children and adolescents, and data on the likelihood of progression to more extensive disease, with a poorer prognosis and a higher cancer risk, have recently been published.[20] In contrast to adults, in whom extension occurs in only 10%, proctosigmoiditis remained stable in only 42% of children. Extension into the descending colon occurred in 20%, into the transverse colon in 12%, and more proximally in the remaining 26%. Extension was unpredictable, but usually occurred within five years of onset.

COLONOSCOPY

Since early descriptions of colonoscopy in infancy and childhood it has become increasingly clear that this investigation is invaluable in the diagnosis and management of inflammatory disease of the colon.[21] The barium enema in this context is now virtually redundant. The procedure is safe and well tolerated, allows multiple mucosal biopsies to be taken, and often adds important information to the diagnosis. For example, over half the patients in a recent study who had endoscopically confirmed colitis had no radiological evidence of inflammatory disease, although only a single contrast barium examination had been used.[22]

DRUG TREATMENT

Sulphasalazine is valuable in the management of ulcerative colitis, particularly as a prophylactic. Side effects, which include reversible male infertility, are common, although probably less troublesome in children. Alternatives to sulphasalazine now exist, and most patients will tolerate mesalazine (delayed release 5-aminosalicylic acid) or olsalazine (altered carrier molecule of salicylate), both of which appear to be as effective as sulphasalazine.[23]

A number of case reports, including two children,[24] and the results of an uncontrolled trial,[25] have recently appeared which suggest that cyclosporin may be useful in patients with severe refractory ulcerative colitis. A controlled trial also suggests a beneficial effect in adults with active Crohn's disease.[26] At present, it is too early to define the precise role of cyclosporin in the management of inflammatory bowel disease, and the results of further trials are awaited, but preliminary results are certainly hopeful.

SURGERY

Although restorative proctocolectomy with an ileal reservoir has offered a highly attractive alternative to an ileostomy, the result is unsatisfactory in 5–10% of children and young adults because of excessive stool frequency and/or faecal incontinence.[27] Moreover, pouchitis, a chronic inflammatory disorder of the ileal reservior producing painful diarrhoea, urgency, and systemic upset, occurs as a long term complication in up to 20% of patients. The long term risks of mucosal dysplasia and neoplasia are uncertain.[28]

Newer forms of inflammatory bowel disease

ALLERGIC COLITIS

Food allergy is an important cause of colitis in the first few months of life.[29] It usually follows a benign course, and most foods are tolerated by 5 years of age.[30] It has been reported in preterm infants, in whom toxic dilatation of the colon can occur.[31] Interestingly, abnormalities after cows' milk challenge may be found in both the jejunum and the rectum of infants with cows' milk sensitive enteropathies.[32] In some infants the abnormality may be expressed only in the colon and not in the proximal small intestine.

Allergic colitis should be suspected in any infant, including a neonate in whom necrotising enterocolitis is an important differential diagnosis,[33] who presents with blood in the stool with or without diarrhoea. A family history of atopy, an eosinophilia, raised serum IgE concentration and positive radioallergosorbent tests are common, but the diagnosis rests upon prompt resolution of symptoms after antigen withdrawal. It is worth noting that the disorder has been described in exclusively breast fed infants.[34] Endoscopy is useful and permits mucosal biopsy. The specimen usually shows an acute and chronic inflammatory cell infiltrate of mainly plasma cells and eosinophils in the lamina propria. Cows' milk is nearly always the offending antigen, but intolerance to soya and beef have been described.

COLLAGENOUS AND MICROSCOPIC COLITIS

Patients have recently been described who present with severe diarrhoea, but without blood loss or tenesmus. The colon is macroscopically normal on endoscopy, but histological examination shows appreciable mucosal inflammatory change[35] sometimes with collagenous thickening of the basement membrane.[36] However the existence of collagenous colitis as a separate pathological entity remains somewhat cotroversial. Patients seem to respond to conventional medical treatment.

MISCELLANEOUS DISORDERS

New associations between colitis and systemic disorders have recently been reported in Behçet's syndrome[37] and hypereosinophilic syndrome.[38] Both children reported with Behçet's colitis required subtotal colectomy. The colitis in hypereosinophilic syndrome was steroid responsive.

1 Rose JDR, Roberts GM, Williams G, Mayberry JF, Rhodes J. Cardiff Crohn's disease jubilee: the incidence over 50 years. *Gut* 1988;**29**:346–51.

2 Koletzko S, Sherman P, Corey M, Griffiths A, Smith C. Role of infant feeding practices in development of Crohn's disease in childhood. *BMJ* 1989;**298**:1617–8.

3 Jenkins AP, Treasure J, Thompson RPH. Crohn's disease presenting as anorexia nervosa. *BMJ* 1988;**296**:699–700.

4 Lenaerts C, Roy CC, Vaillancourt M, Weber AM, Morin CL, Seidman E. High incidence of upper gastrointestinal tract involvement in children with Crohn disease. *Pediatrics* 1989;**83**:777–81.

5 Mashako MNL, Cezard JP, Navarro J, *et al*. Crohn's disease lesions in the upper gastrointestinal tract: correlation between clinical, radiological, endoscopic, and histological features in adolescents and children. *J Pediatr Gastroenterol Nutr* 1989;**8**:442–6.

6 Kleinman RE, Balistreri WF, Heyman MB, *et al*. Nutritional support for pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1989;**12**:8–12.

7 Barton JR, Ferguson A. Failure to record variables of growth and development in children with inflammatory bowel disease. *BMJ* 1989;**298**:865–6.

8 Puntis JWL, Tarlow MJ, Raafat F, Booth IW. Crohn's disease of the lung. *Arch Dis Child* 1990;**65**:1270–1.

9 Scully C, Cochran KM, Russell RL, *et al*. Crohn's disease of the mouth: an indicator of intestinal involvement. *Gut* 1982;**23**:198–201.

10 Field EA, Tyldesley WR. Oral Crohn's disease revisited—1 10-year-review. *Br J Oral Maxillofac Surg* 1989;**27**:114–23.

11 O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *BMJ* 1984;**288**:1859–62.

12 Teahon K, Bjarnason I, Pearson M, Levi AJ. Ten years' experience with an elemental diet in the management of Crohn's disease. *Gut* 1990;**31**:1122–37.

13 Sanderson IR, Udeen S, Davies PSW, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child* 1987;**62**:123–7.

14 Giaffer MH, North G, Holdsworth CD. Controlled trial of polymeric versus elemental diet in treatment of active Crohn's disease. *Lancet* 1990;**335**:816–9.

15 Kirschner BS. Nutritional consequences of inflammatory bowel disease on growth. *J Am Coll Nutr* 1988;**7**:301–8.

16 Belli DC, Seidman E, Bouthillier L, *et al*. Chronic intermittent elemental diet improves growth failure in children with Crohn's disease. *Gastroenterology* 1988;**94**:603–10.

17 Aiges H, Marcovitz J, Rosa J, Daum F. Home nocturnal supplemental naso-gastric feedings in growth retarded adolescents with Crohn's disease. *Gastroenterology* 1989;**97**:905–10.

18 McLain BI, Davidson PN, Stokes KB, Beasley SW. Growth after growth resection for Crohn's disease. *Arch Dis Child* 1990;**65**:760–2.

19 Davies G, Evans CM, Shand WS, Walker-Smith JA. Surgery for Crohn's disease in childhood: influence of sites of disease an operative procedure on outcome. *Br J Surg* 1990;**77**:891–4.

20 Mir-Madjilessi DH, Michener WM, Farmer RG. Course and prognosis of idiopathic ulcerative proctosigmoiditis in young patients. *J Pediatr Gastroenterol Nutr* 1986;**5**:570–5.

21 Williams CB, Laage NJ, Campbell CA, *et al*. Total colonoscopy in children. *Arch Dis Child* 1982;**57**:49–53.

22 Holmquist L, Rudic N, Ahren C, Fallstrom SP. The diagnostic value of colonoscopy compared with rectosigmoidoscopy in children and adolescents with symptoms of chronic inflammatory bowel disease of the colon. *Scand J Gastroenterol* 1988;**23**:577–84.

23 Robinson MG. New oral salicylates in the therapy of chronic idiopathic inflammatory bowel disease. In: Ginsberg AI, ed. *Gastroenterology Clinics of North America. Management of inflammatory bowel disease* 1989;**18**:43–50.

24 Hyams JS, Treem WR. Cyclosporin treatment of fulminant colitis. *J Pediatr Gastroenterol Nutr* 1989;**9**:383–7.

25 Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet* 1990;**336**:16–9.

26 Brynskov J, Freund L, Rasmussen SN, *et al*. A placebo-controlled, double-blind, randomized trial of cyclosporin therapy in active chronic Crohn's disease. *N Engl J Med* 1989;**321**:845–50.

27 Stryker SJ, Telander RL, Perrault J. Anorectal evaluation after colectomy and endorectal ileoanal anastomosis in children and young adults. *J Pediatr Surg* 1985;**20**:656–60.

28 Shepherd NA. The pelvic ileal reservoir: apocalypse later? *BMJ* 1990;**301**:886–7.

29 Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984;**59**:326–9.

30 Hill SM, Milla PJ. Colitis caused by food allergy in infants. *Arch Dis Child* 1990;**65**:132–40.

31 Harrison CJ, Puntis JWL, Durbin GM, Gornall P, Booth IW. Atypical allergic colitis in pre-term infants. *Acta Paediatr Scand* (in press).

32 Inyngkaran N, Yadav M, Boey CG. Rectal mucosa in cows' milk allergy. *Arch Dis Child* 1989;**64**:1256–60.

33 Dupont C, Badoual J, Le Luyer B, Le Bourgeois C, Barbet J-P, Voyer M. Rectosigmoidoscopic findings during isolated rectal bleeding in the neonate. *J Pediatr Gastroenterol Nutr* 1987;**6**:257–64.

34 Perisic VN, Filipovic D, Kokai G. Allergic colitis with rectal bleeding in an exclusively breast-fed neonate. *Acta Paediatr Scand* 1988;**77**:163–4.

35 Sanderson IR, Boyle S, Williams CB, Walker-Smith JA. Histological abnormalities in biopsies from macroscopically normal colonoscopies. *Arch Dis Child* 1986;**61**:274–7.

36 Perisic VN, Kikai G. Diarrhoea caused by collagenous colitis. *Arch Dis Child* 1989;**64**:867–8.

37 Chong SKF, Wright VM, Nishigame T, *et al*. Infantile colitis: a manifestation of intestinal Behçet's syndrome. *J Pediatr Gastroenterol Nutr* 1988;**7**:622–7.

38 Falade AG, Darbyshire PJ, Raafat F, Booth IW. Hypereosinophilic syndrome in childhood presenting as inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* (in press).

Archives of Disease in Childhood 1991; **66**: 745–748

AUDIT

Outcome measures in child health

Stuart Logan

Deparment of Paediatric Epidemiology, Institute of Child Health, 30 Guilford Street, London WC1N 1EH

Correspondence to:
Dr Logan.

In recent years there has been a welcome change in the attitudes of doctors to service evaluation. This has resulted from increased awareness that financial resources are limited and can no longer be allocated on the basis of doctors' magisterial pronouncements. In addition, the radical critics of modern medicine have produced powerful arguments to support their contention that medicine has had little impact on the health of populations.[1–3] In response to these pressures it has become fashionable to emphasise the importance of measures of health outcome in the evaluation of health services. Paediatricians have been quick to respond and both the Community Paediatric Group and the British Paediatric Association (BPA) have produced reports recommending the use of outcome measures in the routine evaluation of paediatric services.[4 5]

At first glance it seems sensible to assess the usefulness of health services by measuring their effects on health. In ideal circumstances this is true but this approach has problems. Firstly, the link between services and health outcomes is usually tenuous because, within a given population, both the incidence and outcome of most conditions depend on host and environmental factors so that services can seldom be expected to have more than a small effect. This is true even for some of our most effective interventions. For instance, the major decline in the incidence and case fatality rates of most infectious diseases occurred before the availability of either prevention or treatment, and the greatest improvements in neonatal mortality preceded the introduction of intensive care. Secondly, most proposed outcome measures entail counting adverse outcomes, which in our society are fortunately rare in childhood. This means that without looking at very large populations it is seldom possible to distinguish real changes from those that happen by chance.

The BPA report *Outcome Measures for Child Health* attempted to produced a blueprint for use by district health authorities.[5] In this paper I will discuss some of the outcome measures recommended in this report, as they illustrate the problems encountered when health outcome measures are used for routine service evaluation. A list of 14 measures has been drawn up 'which health districts or boards (DHAs) can use to monitor their own performance from year to year and to compare themselves with other DHAs'. Eleven of the 14 are health outcome measures (six are 'implied' outcome measures, considered surrogates for actual health outcomes) and three are descriptions of patterns of service that might have adverse health consequences (table 1). Only five of the 11 outcome and implied outcome measures might be useful for monitoring performance over time or for comparing districts, and of these three must be interpreted with caution (table 2).

Where expected numbers are quoted these are figures for England and Wales with 680 000 births/year and a child population of 10 000 000 distributed among 200 district health authorities.

Neonatal and day 1 mortality rates

These rates should be made available by all district health authorities, but as a measure for

Table 1 Proposed health outcome measures for DHAs[5]

- Health outcome measures:
  - Day 1 and neonatal mortality (in four birthweight bands)
  - Notifications of measles and pertussis
  - Asthma admissions lasting over 72 hours
- 'Implied' outcome measures:
  - Late fitting of hearing aids for congenital deafness
  - Late recognition of congenital dislocation of the hip, congenital hypothyroidism, and developmental problems
  - Immunisation uptake
  - The proportion of children with insulin dependent diabetes mellitus whose control is poor (as measured by glycated haemoglobin concentrations
- Descriptions of patterns of service:
  - Proportion of admissions of children <13 who are admitted to adults wards
  - Proportions of operations for hernia and squint that are done as day cases

Table 2 Problems associated with proposed outcome measures for use by DHAs

Measurement	*Problem*	
	Link between service and outcome uncertain or likely to be limited	*Small numbers*
Useful:		
Immunisation coverage	No	No
Admissions for asthma	No	No
Useful but interpret with caution:		
Notifications of measles and pertussis	No	No
Late recognition of developmental problems	No	No
Not useful in this form:		
Neonatal mortality	Yes	Yes
Mortality on day 1	Yes	Yes
Late fitting of hearing aids	No	Yes
Late recognition of congenital dislocation of hips	No	Yes
Congenital hypothyroidism	No	Yes
'Poor control' of insulin dependent diabetes mellitus	Yes	Yes

monitoring the effects of neonatal care they are less useful than might be imagined. Although it is generally believed that neonatal intensive care improves neonatal mortality rates, this has been difficult to show even in quite large studies.[6] This is not because neonatal care has no effect but probably because the main determinants of neonatal mortality have had their effects before birth.

The most powerful risk factor for neonatal mortality is low birth weight, the prevalence of which is known to be closely related to social class. In an attempt to overcome the effects of differences in social class distribution when comparing district health authorities, it was suggested that these rates should be banded according to birth weight. Even within birthweight bands, however, there are social class gradients: the neonatal mortality rate in 1987/1000 livebirths in babies weighing above 3000 g ranged from 1·09 in social class I to 2·35 in social class V, and in babies born weighing <1500 g from 250 to 400, respectively.[7] In evaluating service effects, residual confounding by social class therefore makes comparisons between district health authorities difficult to interpret. As a measure of the health of the population the overall mortality rates may be more helpful, although cumulative figures over some years may be needed so that the number of deaths on which the rates are based is sufficient.

In 1987 there were 3417 neonatal[7] and about half that number of day 1 deaths in England and Wales—an average of 17 neonatal and eight day 1 deaths/district health authority/year. Banding by birth weight removes some of the confounding effect of social factors, but this gain is at the expense of reducing the number of deaths on which each rate is calculated. Among infants weighing 2500 g or more there would be about five neonatal deaths/average district health authority. Using a three year average increases the number of deaths from which the rate is calculated, although it may have the theoretical effect of delaying the recognition of real changes. The expected distribution of the number of deaths in three years/average district health authority population would therefore approximate to a Poisson distribution with a mean of 15: the 95% confidence interval (CI) of this distribution ranges from 8 to 23. Only a figure that fell outside this range could be interpreted as reflecting a real rather than chance difference.

Immunisation coverage and notification rates

Immunisations against measles, diphtheria, and pertussis are extremely effective and coverage rates are an appropriate implied outcome measure of an immunisation programme.

Notifications of infectious diseases are useful for two reasons; they may alert professionals to outbreaks of disease and they may identify groups of children who have been missed by the system. It is important, however, that these figures should be interpreted with caution; notifications are heavily dependent on the interest and enthusiasm of local doctors. It has been estimated that only 40–60% of cases of measles and 5–25% of cases of pertussis are actually notified.[8] An area with a more enthusiastic child health service may paradoxically have a higher than average rate of notifications of infectious diseases because a higher proportion of cases are notified. In addition, the epidemic nature of measles and pertussis results in a variation in incidence from year to year irrespective of immunisation levels, until the coverage is extremely high.

A large increase in notifications should trigger investigation of which children are becoming ill, and why. It is not a statistic that can easily be used to compare the relative efficacy of immunisation programmes over time or in different areas.

Late diagnosis of sensorineural hearing loss, congenital dislocation of the hip, and congenital hypothyroidism

Ideally, when monitoring a screening programme both the false negative and false positive rates should be measured. In a programme designed to detect low prevalence of a condition in a district health authority, however, the false negative rate is unlikely to be useful.

The prevalence of bilateral sensorineural hearing loss (>60 dB mean loss in the better ear) in infancy is about 1/1000 infants.[9] The average district health authority would therefore expect three and a half affected children each year. Using a three year average would mean drawing inferences about the proportion of the 10 or so children who were diagnosed late. When dealing with such small numbers it is intuitively obvious that the proportion diagnosed late is likely to vary by chance. A district health authority might have a poor screening programme, but nine out of 10 cases might still be detected early over a three year period because, by chance, most of the affected individuals in that period came from either a high risk group screened in hospital or had alert parents. The reverse is equally easy to imagine. This difficulty with small numbers also applies to assessing screening programmes for congenital dislocation of the hip (estimates of prevalence vary widely according to the definition used; the reported prevalence of established disease ranges from 0·67/1000[10] to 1·28/1000 live births[11]) and congenital hypothyroidism (prevalence about 1/4000 infants,[12] that is, less than one expected case/year in the average district health authority).

Management of insulin dependent diabetes melitus

The suggested measure here is the proportion of children with diabetes who have glycated haemoglobin (HbA_1) concentrations more than 1·5 times mean for the normal range in that area.

The main problem with this measure is that the effect of services are likely to be less important than the effect of other factors such as the age of the children and their social environment. Before puberty, children with insulin dependent diabetes mellitus tend to have considerably lower levels of HbA_1 than older children (D Dunger, personal communication). The age distribution of cases both in district health authorities and in one district health authority over time will show a random variation, which is likely to be the main determinant of mean concentrations for that district health authority.

The precise number of children with insulin dependent diabetes mellitus in the United Kingdom is not known, but cumulative prevalence figures from the 1958 British birth cohort study suggest a total of roughly 4500 children.[13] With an apparent trend towards a younger age of onset in recent years, the true figure might be nearer 9000.[14] In an average district health authority there would therefore be about 50 children affected. Assuming that half of these children have concentrations of HbA_1 $>1\cdot5$ times the mean of the normal range, and that (following the authors' suggestion), they are divided into two groups according to time since diagnosis, we can expect the number of children across the country in each group who fall into the category defined as 'unacceptable' to follow a Poisson distribution with a mean of 12. The 95% CI for this distribution is between 6 and 20. This implies that only values outside this range could reasonably be ascribed to real rather than chance variations.

Late recognition of developmental problems

As the report acknowledges, differences in practice make this measure useful only within a single district health authority but even here changes over time may be difficult to interpret.

Management of asthma

The collection of data on rates of admission of children with severe asthma is an exciting suggestion that could potentially yield valuable information. Asthma is an important condition that affects a large number of children, many of whom are admitted to hospital each year.

The suggested measure will reflect not only the prevalence of severe disease but also local management of asthma and perhaps ease of access to medical facilities. None the less, most would agree that a decline in such admissions would probably reflect desirable underlying changes.

Discussion

I have discussed some of the difficulties that would be encountered when using the outcome measures propose by the BPA working party. It is not improved outcome measures that are required, however, but a different approach. The first step is to define the aims of monitoring the service. In my view the principle aim of monitoring child health services in a district health authority is to establish whether policies are being implemented and implemented efficiently. The wider question of whether a medical intervention actually improves health belongs to a different level of evaluation. This would require research studies designed to answer specific, and usually fairly limited, questions. Such studies frequently demand separate staff and funding and often need to be multicentre. Research workers do not evaluate the efficacy of a drug simply by observing what happens in different areas, and there is no justification for requiring a less rigorous approach to other interventions.

The managers of a district service need to consider the results of properly designed research evaluations of specific interventions when establishing a policy. Where appropriate studies do not exist, all the information available must be considered in the light of common sense and an interim decision made. Unfortunately most child health services fall into this 'unknown' category. This is not an argument for trying to evaluate their effects on health, district by district, which would be ineffective, but instead to set up studies that will produced answers.

When setting up a system for monitoring child health services the following points should be considered:

- Are the aims of the service and of monitoring clearly set out and accepted by staff?
- Are there clear lines of responsibility for the monitoring excercise and have channels been established that permit the results to lead to change?
- As far as specific measures are concerned:
  (i) Is the measure chosen an adequate reflection of whether a service is fulfilling its aim?
  (ii) Is the measure valid (does it measure what it purports to measure)?
  (iii) Are the data obtainable at a reasonable cost?
  (iv) Are the numbers large enough to distinguish between real change and random fluctuation?
  (v) Is it possible to disentangle the effects of the services on the measure from the effects of other factors?

For some services there is sufficient evidence of the efficacy of the intervention for process measures to serve as implied outcome measures, the obvious example being immunisation. In other circumstances we await the definitive evidence and must establish policy on the balance of probabilities, but here again process measures are usually appropriate.

When dealing with uncommon conditions I have argued that it is not appropriate to use the rate of adverse outcomes or, in the case of screening programmes, the false negative rate, to evaluate the service. This does not mean that one ignores these cases. To gain the most information about possible gaps in the service it is important to look at these cases individually, not as numbers. Any child with sensorineural hearing loss who has not been identified by 15 months of age represents a failure and requires investigation. The same is true of a child with a late diagnosis of congenital hypothyroidism. This principle is widely accepted by neonatologists who routinely hold meetings to discuss the children who die on their units; there is no reason why the same should not be true of other paediatric services. While such investigations can become witch hunts this is not inevitable, and they can be a useful means of identifying unsuspected flaws.

As a general principle, the use of health outcomes as a measure of the effects of services at a district level can only occasionally be helpful. What is needed in child health (as in other branches of medicine) is: firstly, the establishment of a clear set of goals for the service that can be translated into concrete objectives and, secondly, the development of a set of research priorities with funding set aside for properly designed studies to answer central questions about service efficacy.

1 Illich I. *Limits to medicine. Medical nemesis: the expropriation of health.* Harmondsworth: Penguin, 1978.

2 Doyal L. *The political economy of health.* London: Pluto, 1979.

3 Navarro V. *Medicine under capitalism.* London: Croom Helm, 1976.

4 Allsop M, Colver A, McKinlay I. *Measurement of child health.* London: Community Paediatric Group, 1987.

5 Report of the Outcome Measures Working Party. *Outcome measurements for child health.* London: British Paediatric Association, 1990.

6 Forbes JF, Larssen K-E, Leiv S. Access to intensive neonatal care and neonatal survival in low birthweight infants: a population study in Norway. *Paediatric and Perinatal Epidemiology* 1987;1:33–42.

7 Office of Populations Censuses and Surveys. *Mortality statistics. Perinatal and infant: social and biological factors.* DH3 No. 21. London: HMSO, 1987.

8 Clarkson JA, Fine PEM. The efficiency of measles and pertussis notification in England and Wales. *Int J Epidemiol* 1985;**14**:153–68.

9 Peckham CS. Hearing impairment in childhood. *Br Med Bull* 1986;**42**:145–9.

10 McKeown T, Record RG. Malformations in a population observed for five years after birth. In: Wolstenholme GEW, O'Connor CM, eds. *Ciba foundation symposium on congenital malformations.* London:Churchill, 1960:2–16.

11 Catford JC, Bennet GC, Wilkinson JA. Congenital hip dislocation: an increasing and still uncontrolled disability. *BMJ* 1982;**285**:1572–30.

12 Grant DB, Smith I. Survey of neonatal screening for primary hypothyroidism in England, Wales and Northern Ireland. *BMJ* 1988;**296**:1355–8.

13 Stewart-Brown S, Haslum M, Butler N. Evidence for increasing prevalence of diabetes mellitus in childhood. *BMJ* 1983;**286**:1855–7.

14 Kurtz Z, Peckham CS, Ades AE. Changing prevalence of juvenile-onset diabetes mellitus. *Lancet* 1988;ii:88–90.

Children in disasters

A recent article in the *Journal of the Royal Society of Medicine* (W Yule, 1991;**84**:12–5) describes reactions seen in children who have survived disasters, in particular, the Zeebrugge disaster and the sinking of the cruise ship Jupiter in Athens. Some 30–50% of children show significant evidence of continuing disorder for months after the disaster and the problems are not always recognised by parents or teachers. They include depression, sleep disturbance, difficulties in separating from the parents, defects of memory and concentration leading to poor school performance, irritability, guilt feelings, panic attacks, fear of water or of travel, and difficulties in communication with parents or peers.

These children need professional help. For a discussion of their treatment Dr Yule refers readers to his chapter in a new book.[1]

ARCHIVIST

[1] Yule W. Work with children following disasters. In: Herbert M, ed. *Clinical child psychology: theory and practice.* Chichester: Wiley, 1991.

Archives of Disease in Childhood 1991; **66:** 749–753

LETTERS TO THE EDITOR

Tests for growth hormone secretion

SIR,—Professor Brook and Dr Hindmarsh claim that children growing at a less than 3rd centile velocity carry a 97% chance of showing an abnormality on investigation.[1] In a leading article in the *British Medical Journal* in 1986 they wrote 'If a third centile velocity is chosen for immediate action the chances of investigating a normally growing child are only 3%'.[2] The latter statement is capable of two interpretations. It could mean that 3% of normal children would be investigated, which is true. It could also be taken to mean that 3% of investigated children would be normal, which is not true, unless by chance. Only this second interpretation, however, fits with the assertion that 97% of investigated children would be abnormal.

The percentage of children below the third centile who are abnormal is:

$$\frac{\text{Number of abnormal children in the group (<3rd centile)}}{\text{Total number of abnormal + normal children in the group}} \times 100$$

Growth chart centiles concern only normal children. They cannot tell us about the number, or even the existence, of abnormal children and therefore cannot provide the figures necessary for the calculation.

The chances of finding an abnormality on investigation depend on the sensitivity of the methods of investigation, and on what proportion of those perceived as having the problem have a pathological cause for it and what proportion represent simply the extremes of biological variability. Brook and Hindmarsh give no indication that they have taken these factors into account in arriving at their figure of 97%.

D P ADDY
*Dudley Road Hospital,
Dudley Road,
Birmingham B18 7QH*

1 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;**66:** 85–7.
2 Brook CGD, Hindmarsh PC, Healy MJR. A better way to detect growth failure. *BMJ* 1986; **293:**1186.

Professor Brook and Dr Hindmarsh comment
We thank Dr Addy for his interest and we accept his point.

In practical terms it makes not the slightest difference because the total number of abnormal children will so greatly outweigh the number of normal children that the fraction he gives will approach unity or 100%, which is the point we were trying to make.

Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin

SIR,—The paper by Coombs *et al* claims to show indomethacin has direct effects on the splanchnic circulation that are independent of its desired effect, that is, closure of the duct.[1] Indomethacin is such a widely used and important drug that such a claim must be carefully evaluated.

The observed effects of drug administration were a decrease in systolic gut flow velocity with a change to antegrade diastolic flow by one hour. In the group given a rapid bolus the systolic velocity fell further and more rapidly; it is claimed that this is due to splanchnic vasoconstriction. The evidence provided does not support this. The conclusions are presumably based on the assumption that left ventricular stroke volume does not change after indomethacin administration. In fact several papers have shown that left ventricular stroke volume falls dramatically, with a fall in systolic aortic velocity, if the duct closes.[2–4] An abnormally raised cardiac output returns to normal. The decrease in systolic mesenteric flow velocities observed in this study could therefore merely reflect aortic flow changes secondary to rapid ductal constriction. The observed velocity changes could have occurred in the descending aorta, the renal arteries, and even the femoral arteries,[2] in fact in any systemic artery. Indomethacin normally closes the duct; therefore, to study its generalised effects, the haemodynamic consequences of ductal constriction must be taken into consideration. The observation that the fall in gut flow velocities decreases with second and third doses could be explained by the duct becoming progressively smaller and therefore the haemodynamic consequences of ductal constriction becoming less marked.

The suggestion that rapid administration of indomethacin causes an undesirable fall in splanchnic circulation is probably a misinterpretation of the observations presented in this paper. We note that none of the 19 infants given indomethacin suffered serious side effects and that, in every case, retrograde or absent diastolic flow changed to normal antegrade flow.

JONATHAN R SKINNER
JEAN MATTHES
EDMUND N HEY
*Department of Child Health,
Princess Mary Maternity Hospital,
Great North Road,
Newcastle upon Tyne NE2 3BD*

STEWART HUNTER
*Department of Paediatric Cardiology,
Freeman Hospital,
Newcastle upon Tyne NE7 7DN*

1 Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. *Arch Dis Child* 1990;**65:**1067–71.
2 Alverson DC, Eldridge MW, Johnson JD, *et al.* Effect of patent ductus arteriosus on left ventricular output in premature infants. *J Pediatr* 1983;**102:**754–7.
3 Hirsimaki H, Kero P, Wanne O, *et al.* Doppler-derived cardiac output in healthy newborn infants in relation to physiological patency of the ductus arteriosus. *Pediatr Cardiol* 1988;**9:** 79–83.
4 Lindner W, Seidel M, Versmold HT, Döhlemann, Riegel KP. Stroke volume and left ventricular output in preterm infants with patent ductus arteriosus. *Pediatr Res* 1990;**27:** 278–81.

Hyperinsulinaemic hypoglycaemia in small for dates babies

SIR,—The paper by Collins *et al* on hypoglycaemia in the small for dates infant raises two important issues about the pathogenesis and hence management of such infants.[1] The authors suggested that the low glucose concentration in the subgroup without overt evidence of hyperinsulinsm might be explained by a transient deficiency in glucagon secretion.[2] This implies that they believe that the remaining infants had normal plasma glucagon concentrations. However is it not equally likely that a proportion of their 'hyperinsulinaemic' group were also relatively deficient in this vital gluconeogenic hormone? Thus could not the persistence of the fetal insulin effect be due to a failure of the normal postnatal surge in glucagon release? In the absence of glucagon, the key enzymes of the gluconeogenic pathway (for example, phosphoenol pyruvate carboxykinase) would be inoperative and it has recently been shown that glucose-6-phosphatase also requires glucagon for catalytic activity.[3]

The second and related issue is that given the wealth of theoretical evidence of the potential importance of this hormone, why is the glycaemic response so poor after an intramuscular injection? In pilot studies before the original paper on transient glucagon deficiency,[2] I observed that infants who failed to respond to intramuscular glucagon nevertheless showed a brisk, sustained rise in peripheral plasma glucose concentration after an intravenous bolus (200 µg/kg). The most likely explanation is that the sustained peak plasma concentrations of this hormone after intravenous injection might be sufficient to raise the concentration in the portal vein above the local insulin concentrations and thereby reverse the direction of net hepatic glucose flux. Thus the early use of intravenous glucagon in all hypoglycaemic infants is likely to shorten their dependence on intravenous glucose supplementation and in addition prevent rebound hypoglycaemia when oral feeding is introduced.

ANIL MEHTA
*Department of Child Health,
Ninewells Hospital and
Medical School,
Dundee DD1 9SY*

1 Collins JE, Leonard JV, Teale D, *et al.* Hyperinsulinaemic hypoglycaemia in small for dates babies. *Arch Dis Child* 1990;**65:**1118–20.
2 Mehta A, Wootton R, Cheng KN, Penfold P, Halliday D, Stacey TE. Effect of diazoxide or glucagon on hepatic glucose production rate during extreme neonatal hypoglycaemia. *Arch Dis Child* 1987;**62:**924–30.
3 Burchell A. The molecular pathology of glucose 6 phosphatase. *FASEB J* 1990;**4:**2978–88.

Drs Collins, Leonard, Teale, and Marks comment:
We thank Dr Mehta for his letter. In the original protocol it was planned to measure plasma glucagon concentrations in all the babies, but there was insufficient blood in all but a few samples for us to do this. In two patients who were hyperinsulinaemic (cases 6 and 9) glucagon was not detectable in plasma at the time of hypoglycaemia (limit of detection 25 pmol/l). These results are consistent with the hypothesis that the hyperinsulinaemic babies were relatively glucagon deficient as well.

Development of intestinal motility

SIR,—In Dr Bisset's article on development of intestinal motility he notes that little is known of the development of colonic motility in humans and that most infants pass their first bowel motion during either labour or the ensuing 48 hours.[1] While this is true there is a very noticeable gestational age effect on the passing of meconium by a fetus during labour which gives some idea of the maturation of this aspect of gut function. Increasing gestational age is by far the strongest predictor of the presence of meconium in amniotic fluid at delivery with 10% of infants at 35 weeks' gestation, 17% at 40 weeks' gestation, and 25% at 42 weeks' gestation having passed meconium before delivery.[2] The presence of meconium in labour before 34 weeks' gestation is uncommon and infections such as listeria need to be excluded. The mechanism resulting in the passage of meconium is unknown but has been said to depend on hypoxia or acidosis,[3] with vasoconstriction of the fetal intestinal blood supply, hyperperistatis, and anal spincter relaxation.[4] However it seems highly likely that the passage of meconium is generally a normal physiological event reflecting increasing fetal maturity.

S M GORMALLY
T G MATTHEWS
Department of Paediatrics,
The Rotunda Hospital,
Dublin 1,
Republic of Ireland

1 Bisset WM. Development of intestinal motility. *Arch Dis Child* 1991;66:3–5.
2 Matthews TG, Stack JC, Unwin AR, Harrison RF. Is there a gestational age distribution in the passage of meconium. *Journal of Obstetrics and Gynaecology* 1983;4:23–4.
3 Walker J. Fetal anoxia. *Journal of Obstetrics and Gynaecology of the British Empire* 1954;**61**: 162–80.
4 Saling E. *Fetal and neonatal hypoxia in relation to clinical obstetrical practice.* London: Arnold 1968:117.

Gastro-oesophageal reflux in apparent life threatening events

Sir,—Your editorial on surgery for gastro-oesophageal reflux stated that apparent life threatening events (ALTE or 'near miss' SIDS episodes) associated with confirmed gastro-oesophageal reflux was 'probably an absolute' indication for surgery.[1] While having some difficulty with the concept of probable absolutes the following points should be noted.

Gastro-oesophageal reflux is a common event in infants and the application of techniques such as continuous lower oesophageal pH measurement has resulted in its association with a variety of conditions from asthma, recurrent bronchitis, pneumonia, apnoeic periods in the newborn, cyanotic attacks, ALTE, rumination, torticollis, abnormal movements of the head and neck, and neuropsychiatric disorders.[2] However as Carré previously noted none of these disorders, with the exception of pulmonary infections, occurred with increased frequency in a 35 year prospective study of 710 children with partial thoracic stomach (hiatal hernia) and gastro-oesophageal incompetence.[2]

The presence of gastro-oesophageal reflux in infants who have suffered an ALTE does not establish a causal relationship. Before embarking on surgical treatment of a common, and usually harmless, condition it is imperative that a clear association be established between the two events—that is, it has to be shown that gastro-oesophageal reflux causes the ALTE in a particular child. Previous studies do not support surgical intervention with no clear causal relationship established and no benefit from fundoplication.[3]

Even if gastro-oesophageal reflux is shown to cause an ALTE in an infant we should perhaps ponder on why this infant reacts so differently from the majority of infants with gastro-oesophageal reflux.

At present the role of gastro-oesophageal reflux in ALTE is still unclear and needs to be firmly established before the various management options (including medical and conservative) can be prospectively evaluated.

S M GORMALLY
T G MATTHEWS
Department of Paediatrics,
The Rotunda Hospital,
Dublin 1,
Republic of Ireland

1 Kiely EM. Surgery for gastro-oesophageal reflux. *Arch Dis Child* 1990;65:1291–2.
2 Carré IJ. Clinical significance of gastro-oesophageal reflux. *Arch Dis Child* 1984;59: 911–2.
3 Rosen CL, Frost JD, Harrison GM. Infant apnoea: polygraphic studies and follow-up monitoring. *Pediatrics* 1983;71:731–6.

Nutrition and bronchopulmonary dysplasia

Sir,—We read the article by Wilson *et al* on nutrition and bronchopulmonary dysplasia[1] with interest and should like to report some of our own data for comparison. Between January 1980 and December 1989, 4389 infants under 72 hours of age have been admitted to the neonatal intensive care unit at Liverpool Maternity Hospital. Two hundred and forty two of these developed bronchopulmonary dysplasia, which was defined as being present if an infant had received ventilatory support for over 24 hours in the first 72 hours of life and had a persistent requirement for supplementary oxygen together with an abnormal chest radiograph on day 28. We performed a multiple logistic regression analysis of these data with bronchopulmonary dysplasia as the dependent variable and sex, birth weight, gestation, survival to discharge, and year of birth as independant variables. This showed an inverse correlation between the occurrence of bronchopulmonary dysplasia and birth weight which was independent of gestational age (odds ratio for a rise of 250 g in birth weight above 500 g=0·83; 95% confidence interval=0·77 to 0·90).

We have also investigated in detail the growth of nine infants with severe bronchopulmonary dysplasia who have recently been discharged from hospital receiving supplementary oxygen. Of the six that had been born at more than 28 weeks' gestation only two were below the 3rd centile for weight at birth, three were between the 10th and 50th, and one was above the 90th. At term all nine infants were below the 3rd centile for weight and at discharge from hospital eight were still below the 3rd centile.

The above findings are in agreement with those of Wilson *et al* and lend strong support to the hypothesis that infants who develop bronchopulmonary dysplasia fail to achieve optimal growth postnatally as well as antenatally.

N J SHAW
R W I COOKE
Department of Child Health,
Liverpool Maternity Hospital,
Oxford Street,
Liverpool L7 7NB

1 Wilson DC, McClure G, Halliday HL, Reid M McC, Dodge JA. Nutrition and bronchopulmonary dysplasia. *Arch Dis Child* 1991;66: 37–8.

Continued need for pneumococcal prophylaxis after splenectomy

Sir,—In a recent issue of this journal Drs Murdoch and Dos Anjos reported two children who died of overwhelming pneumococcal infection, five and eight years after splenectomy.[1] They might have included in their report a patient at Guy's Hospital who died last summer 30 years after splenectomy performed at the age of 2 years at the Evelina Children's Hospital.

The girl was admitted to the Evelina Children's Hospital in 1959 when I was paediatric registrar. She had idiopathic hypoglycaemia—at that time labelled McQuarrie's syndrome. Heavy doses of steroid controlled her symptoms but rendered her grossly cushingoid. A single insulin estimation (30 ml blood from a femoral vein that was incubated on a rat's diaphragm) showed high circulating insulin concentrations and a subtotal pancreatectomy was carried out. To achieve this it was necessary to remove her spleen. The operation cured her hypoglycaemia and did not cause diabetes mellitis. The child thrived well physically and intellectually.

Some 20 years later, when I met a case of nesidioblastosis, I asked for the original blocks of her pancreas to be brought out, appropriately stained, and confirmed the diagnosis that she also had nesidioblastosis. At a meeting on hypoglycaemia at Guy's Hospital I presented the case history and the 'patient' attended; she was healthy and holding down a good job. The fact of splenectomy was noted but since she was now in her early 20s and very well, no prophylactic penicillin was suggested.

She married, bore two children successfully, and never had any obvious problem with infection. On the summer of her death she became unwell with a high fever and joint pains in the knee. She was seen in Guy's Hospital casualty department where the abdominal scar was attributed to pancreatectomy, and the casualty officer was unaware of the splenectomy. Radiographs were taken and tests were initiated but she was not admitted. In the small hours of that night she was brought in dead to King's College Hospital. Necropsy showed overwhelming infection with *Streptococcus pneumoniae.*

This tragic story, together with other cases encountered in my 30 years as a paediatrician, leads me to endorse Drs Murdoch and Dos Anjos' recommendations on prophylaxis, though they would not have saved the woman described here. (Pneumovax II was not available in 1959 and the infection occurred long after she had passed 'increased epidemiological risk of pneumococcal infection such as school, university, or the armed forces'.) Therefore, prophylactic penicillin should be continued for life. As this will inevitably lead to problems with compliance, an alternative is that the patient should carry a card and always have a large dose of amoxycillin capsules to be taken at once in any sudden feverish systemic illness, and seek medical advice promptly. I would also add that wherever the circumstances allow, Pneumovax II should be given before splenectomy.

J W SCOPES
Department of Paediatrics,
St Thomas's Hospital,
London SE1 7EH

1 Murdoch IA, Dos Anjos R. Continued need for pneumococcal prophylaxis after splenectomy. *Arch Dis Child* 1990;65:1268–9.

Archives of Disease in Childhood 1991; **66:** 751

Eight and 12 week courses of cyclophosphamide in nephrotic syndrome

SIR,—We read with great interest the report on cyclophosphamide treatment of steroid dependent nephrotic syndrome recently published in this journal by Ueda *et al.*[1] Surprisingly the authors could not find any difference in the number of patients who remained in sustained remission after treatment with cyclophosphamide for either eight or 12 weeks, contrary to our previous finding.[2] We would like to comment on the conclusions of this study, as we find considerable differences in the treatment procedures used in their study and ours, in addition to the age differences in patients described by the authors.

Most notable is the difference in the *initial* treatment of nephrosis. All of our patients were treated initially according to the standard treatment protocol of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN), that is, 60 mg/m^2/day continuously for four weeks, followed by treatment on alternate days with 40 mg/m^2/48 hours prednisone. In contrast, the duration of the initial treatment of patients in the study by Ueda *et al* was significantly longer, that is, four weeks of continuous steroid administration, followed by three to four months' treatment with tapered down prednisone dose (reduction of 5 to 10 mg/m^2 every two weeks). Thus the total amount of prednisone in the initial treatment was 2240 mg/m^2 in the APN study, but about 4620 mg/m^2 in the study of Ueda *et al.* It has been shown recently that the intensity of the initial treatment is a critical factor in the outcome and prognosis of steroid sensitive nephrotic syndrome—that is, the longer and more intensive the initial treatment is, the lower the number of patients who relapse, and the number of relapses and frequent relapsers.[3] We therefore would assume that the patients of Ueda and his colleagues represent a highly selective group, who suffer from a more severe nephrotic syndrome than the patients treated by the APN protocol, and where steroid dependency could not be prevented by any intense initial treatment. Otherwise it could not be explained why the cumulative percentage of sustained remission rates after eight or 12 weeks' cyclophosphamide were only 24% or 25%, respectively, which is lower than all other published results of cytotoxic drug treatment for steroid dependent nephrotic syndrome.[4–9] We therefore strongly suggest that the differences in the results of the two studies are due to the selection of patients who were treated with cyclophosphamide. The longer duration of the trial (five years Ueda *et al v* 2 years in the APN study) and the higher number of patients in the study by Ueda *et al* seem to play only a minor part in these results (see table) as all but one of the patients of Ueda *et al* relapsed within two years after treatment with cyclophosphamide. Therefore our study was sufficient to judge the effectiveness of cyclophosphamide treatment, which was later confirmed in a five year evaluation of APN study groups.[10]

In summary, we cannot agree with the general conclusion of Ueda *et al* that the effect of an eight week course of cyclophosphamide appears to be the same as that of a 12 week course in children with steroid dependent minimal change nephrotic syndrome. This is probably only true for such groups of patients who were as intensively treated initially as in the study of Ueda *et al.* For those who were treated less intensively, by the International Study of Kidney Diseases in Children (ISKDC) and APN, our conclusion can be maintained that cyclophosphamide should be used for eight weeks in patients who relapse frequently and are not steroid dependent and for 12 weeks in patients who relapse frequently but are steroid dependent.

B OEMAR
J BRODEHL
Arbeitsgemeinschaft für Pädiatrische Nephrologie,
Department of Pediatric Nephrology
and Metabolic Disease,
Medical School Hannover,
D-3000 Hannover 61,
Federal Republic of Germany

1 Ueda N, Kuno K, Ito S. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. *Arch Dis Child* 1990;**65:**1147–50.
2 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. *Arch Dis Child* 1987;**62:**1102–6.
3 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Minimal change nephrotic syndrome (MCNS): long prednisone therapy versus standard prednisone therapy. *Pediatric Nephrology* 1990;**4:**C60.
4 Brodehl J, Krohn HP, Ehrich JHH. The treatment of minimal change nephrotic syndrome (lipoidnephrosis): cooperative studies of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN). *Klin Padiatr* 1982;**194:**162–5.
5 Barratt TM, Bercowsky A, Osofsky SG, Soothill JF, Kay R. Cyclophosphamide treatment in steroid sensitive nephrotic syndrome of childhood. *Lancet* 1975;**i:**55–8.
6 Cameron JS, Chantler CS, Ogg, White RHR. Long-term stability of remission in nephrotic syndrome after treatment with cyclophosphamide. *BMJ* 1974;**iv:**7–11.
7 Chiu J, Drummond KN. Long term follow-up of cyclophosphamide therapy in frequent relapsing minimal lesion nephrotic syndrome. *J Pediatr* 1974;**84:**825–30.
8 Garin EH, Pryor ND, Fennell RS, Richard GA. Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. *J Pediatr* 1978;**92:**304–8.
9 McDonald J, Murphy AV, Arneil GC. Long-term assessment of cyclophosphamide therapy for nephrosis in children. *Lancet* 1974;**ii:**980–2.
10 Krohn HP, Brodehl J. Cytotoxic drug study I of the APN: 5-year follow-up. *Helv Paediatr Acta* 1986;**41:**107.

Characteristics of steroid dependent patients in study groups

	Ueda et al[1]		*APN*[2]	
	12 Weeks	*8 Weeks*	*12 Weeks*	*8 Weeks*
Male:female	28:13	26:6	7:11	9:9
Mean age at onset of nephrosis (years)	6·40	6·00	5·80	4·90
Mean steroid dose for initial treatment (mg/m^2)	4620	4620	2240	2240
Mean age at entry to cyclophosphamide study (years)	7·80	7·70	8·60	6·90
Mean duration of nephrosis before cyclophosphamide (months)	19·20	18·80	34·80	22·80
No of relapses (12) or (6) months before entry	5·1 (12)	4·5 (12)	4·4 (6)	4·8 (6)
Total cumulative dose of prednisone before cyclophosphamide (mg/kg/patient/month)	18·50	19·30	27·40	26·40
No of patients with relapse after cyclophosphamide/total patients	31/41	24/32	6/18	14/18
Cumulative % of sustained remission	24	25	67	22

Dr Ueda comments:

I read with interest the comments by Dr Oemar and Professor Brodehl, and I wish to thank them for their thoughtful remarks. There are indeed some differences between their study and ours. However, I cannot agree with the suggestion that we had a highly selective group of patients as a result of different initial steroid treatment, because the remission rate in their patients treated for eight weeks is similar to those reported by us. I might add that the longer steroid treatment seems not to affect the subsequent course when it is used once nephrotic patients are steroid dependent, although this has an impact on the outcome when it is used as initial treatment.[1]

Perhaps the important differences may relate to the criteria for steroid dependence and the age of the patients studied. The criteria for steroid dependence they adopted is somewhat different from ours as they included the patients other than those relapsed while receiving steroids or within 14 days after stopping steroids ('fast' relapser). Such patients could be more responsive to cyclophosphamide than those with 'fast' relapse. In addition, the most striking difference is the age at which cyclophosphamide was instituted. The age at entry into the study of their patients treated for 12 weeks, who had higher relapse free rate, is higher than that of those treated for eight weeks and of our patients with relapse, but is similar to that of our patients without relapse. Cyclophosphamide appears more effective in older patients than in the younger,[2] thus the distribution of the age at entry should be strictly the same in a comparative trial of such a drug. Finally, I am sure that Oemar and Brodehl would agree with me that their data must be interpreted with caution because of the retrospective nature of their study and the small number of patients in their study group. Thus in their study if the only two patients treated for 12 weeks relapsed, the differences in the efficacy of the two regimens would be insignificant.

In summary, if the data including the total time off steroids, the number of the patients without 'fast relapse' before cyclophosphamide, the age at entry into the study of patients with and without relapse, and the recent outcome after the completion of their study are available, the discrepancy between their and our results could be more clarified. We believe that the two regimens have an equivalent efficacy when a patient selection is carefully performed as described above.

1 Udea N, Chihara M, Kawaguchi S, *et al.* Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr* 1988;**112:** 122–6.
2 Barratt TM, Bercowsky A, Osofsky SG, Soothill JF, Kay R. Cyclophosphamide treatment in steroid-sensitive nephrotic syndrome of childhood. *Lancet* 1975;**i:**55–8.

Acute wheezy bronchitis—lumping and splitting

SIR,—Mertsola and colleagues have carried out a very comprehensive and worthwhile study on the association between viral infection and wheezing in childhood.[1] However, their terminology 'wheezy bronchitis' as an appropriate diagnostic term for their study population should be reconsidered. It is an emotive term, and its definition far from clear.

Wheezy bronchitis was originally used to describe preschool children who wheezed only after viral respiratory tract infections and who seemed relatively resistant to sympathomimetic and steroid treatment. It was thought that only a minority of these children went on to develop 'asthma'. With the increasing awareness of the underdiagnosis of asthma in childhood the term was re-examined.[2] Wheezy bronchitis was attacked as an over used euphemism for childhood wheeze. Far from avoiding the diagnosis 'asthma', implying a chronic illness, the use of 'wheezy bronchitis' led to undertreatment and inappropriate use of antibiotics in many true asthmatics. It was suggested that all who wheezed should be lumped together as asthmatic unless proved otherwise. In keeping with this concept most doctors and many parents now perceive asthma as a common condition with a wide range of severity and symptoms throughout childhood.

Last year Dr Nicola Wilson re-examined the idea of splitting up wheezy disorders in childhood.[3] Like Professor Margaret Turner-Warwick, who described different patterns of airflow obstruction in chronic adult asthmatics,[4] she has argued that difficulties in treating asthmatic preschool children related to a failure in identifying clinical subgroups with different patterns of illness. Lacking a better term, she described a splinter group of 'wheezy bronchitics' as children who wheezed only in response to viral infections with little or no atopy compared with asthmatics of the same age. If the term is to be used at all it should refer to these kind of children. This is clearly not the group of patients studied in Finland. Forty three percent of these were highly atopic and atopic features were common in the rest. We are given no information about a family history of atopy. Although viral infections were identified in 45% of respiratory episodes, wheezing occurred in 73% of respiratory episodes in which no virus was found. These children might have had typical asthma with wheeze secondary to precipitants unrelated to viral infections. Thirty nine percent of children were receiving regular prophylaxis. This might have prevented persistent asthma symptoms that would otherwise have been present.

If childhood asthma is to be split up careful attention must be paid to clearly defining separate subgroups. This is particularly important when considering pathogenesis and treatment of airway narrowing in our young wheezers.

G CONNETT
Royal Alexandra Hospital,
for Sick Children,
Dyke Road,
Brighton BN1 3JN

1 Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. *Arch Dis Child* 1991;**66**:124–9.
2 Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *BMJ* 1983;**286**:1253–5.
3 Wilson NM. Wheezy bronchitis revisited. *Arch Dis Child* 1989;**64**:1194–9.
4 Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest* 1977;**71**:73–85.

Drs Mertsola, Ruuskanen, Vanto, et al comment: We appreciate the comments of our colleagues and agree that many of our patients can be regarded as asthmatics. However, according to our present practice, the inclusion criteria used in the study (two or more wheezy bronchitis attacks) do not permit an asthma diagnosis in all these children. At present many authors regard wheezy bronchitis and asthma as the same disorder and children with wheezing attacks are treated with the principles of asthma therapy (as was the case in our study). The use of a term 'wheezy bronchitis' should not lead to undertreatment of patients.

About one third of the children in our study had regular prophylaxis and we agree that this might have prevented wheezing attacks in some children, as discussed in the paper. Recently we re-evaluated the importance of allergen exposure as a cause of wheezing in these children.[1] Although many of the patients were atopic, allergen exposure was not often suspected or proved as a precipitating factor for wheezing. This was probably due to the effective allergen avoidance routinely advised to parents of young children in child health centres in Finland. The early preventive measures are helpful for the patients but make the analysis of these kind of studies even more complex.

1 Vanto T, Ziegler T, Mertsola J, Ruuskanen O, Koivikko A. Allergen exposure and respiratory virus infections in young wheezy children (abstract). *J Allergy Clin Immunol* 1991;**87**:344.

Spontaneous resolution of congenital nephrotic syndrome in a neonate

SIR,—We were interested to read the article by Banton *et al* referring to a baby with congenital nephrotic syndrome whose condition resolved.[1] We too have observed a child with congenital nephrotic syndrome who made a spontaneous recovery, and whose case raises important ethical considerations.

The mother had a raised serum α fetoprotein concentration on routine screening in pregnancy and amniocentesis, performed at 21 weeks' gestation, showed an α fetoprotein concentration of 325 mg/l (normal <20) with normal cholinesterase. An ultrasound scan showed no gross fetal abnormalities. A diagnosis of congenital nephrotic syndrome was made and the mother was offered termination of her pregnancy but declined on religious grounds. A boy was born at term weighing 3750 g, the placenta weighing 1000 g. He had gross proteinuria (Albustix 4+) at birth but no haematuria. He also became hypoalbuminaemic, with a serum albumin of 18 g/l at 2 weeks. He had mild pitting oedema in the first week but none subsequently and at no time did he become hypertensive. The selectivity index (IgG urine : serum as a percentage of transferrin urine : serum ratio) was initially <7% (highly selective proteinuria) but rose to 17% at 7 weeks. The level then fell back to 9% at 10 weeks of age and the proteinuria had resolved by 10 months. A renal biopsy specimen at 2 months of age showed normal glomeruli by light microscopy with the exception of one obsolescent glomerulus. The tubules, interstitium, and blood vessels appeared normal. Immunofluorescent stains for complement components and immunoglobulins were all negative, and these findings were compatible with 'minimal change' nephrotic syndrome. He was treated with a high protein diet (6 g/kg/day), replacement immunoglobulin, and penicillin prophylaxis up to 5 months of age; neither steroids nor diuretics were used. The child is now 6 years old, has not relapsed, and is entirely well.

The congenital nephrotic syndrome is heterogeneous and various types can be recognised histologically. The Finnish type, and the forms exhibiting diffuse mesangial sclerosis, or focal segmental glomerulosclerosis all have a poor prognosis. A policy of prenatal diagnosis is therefore justified in families with a previously affected child whose clinical course or histological type is known to be adverse. However from time to time screening for neural tube defects by maternal α fetoprotein in serum and amniotic fluid will lead unexpectedly to the diagnosis of congenital nephrotic syndrome[2 3] and the type of congenital nephrotic syndrome and the actual prognosis will not be known. In view of the benign course of our patient, and the one described by Banton *et al*, the counselling of such families can be extremely difficult.

A review of patients with congenital nephrotic syndrome at this hospital over a period of 24 years (S Yoshiara, RHR White, F Raafat, unpublished data) showed that, of 26 cases proved at biopsy, eight were of the Finnish type, three had the form exhibiting diffuse mesangial sclerosis, 12 had focal segmental glomerulosclerosis, and three the histological appearances compatible with minimal change nephrotic syndrome. Of the latter, two siblings were steroid resistant and continue to have mild proteinuria at 19 years of age, with normal renal function, although one is hypertensive. The other child responded to prednisolone 60 mg/m^2/day and remained in complete remission until 5 years of age, when proteinuria recurred; a further biopsy specimen taken at this time showed type 1 mesangiocapillary glomerulonephritis. One of the 12 infants with focal segmental glomerulosclerosis was partially steroid responsive and is currently in remission after treatment with cyclophosphamide.

The distinction between the histological subtypes can sometimes present difficulties. Although the glomeruli in Finnish nephrotic syndrome show mild mesangial hypercellularity, this can also be a feature of minimal change nephrotic syndrome. Moreover the cystic tubular dilatation which characterises Finnish nephrotic syndrome is of variable severity and also occurs in focal segmental glomerulosclerosis, while segmental sclerosis in the latter condition may initially be so minimal as to escape detection in a renal biopsy specimen obtained during the first three months of life. Experience in differential diagnosis can only be gained if patients are referred to regional paediatric nephrology centres for evaluation.

If the differential diagnosis remains in doubt, it is reasonable to offer a trial of corticosteroid treatment, with antibiotic prophylaxis because of the increased risk of infection, rather than to dismiss the condition as untreatable. The counselling of a woman who had not previously had a child with congenital nephrotic syndrome requires an awareness that there is, perhaps, as much as a 10% prospect of steroid responsiveness if she produces an affected, liveborn infant.

The authors are grateful to Dr James Partridge for permission to report this patient.

GRAHAM SMITH
MICHAEL WINTERBORN
Department of Nephrology,
East Birmingham Hospital,
Bordesley Green East,
Birmingham B9 5ST

R H R WHITE
The Children's Hospital,
Ladywood Middleway,
Birmingham B16 8ET

1 Banton CR, Thalayasingham B, Coulthard MG. Spontaneous resolution of congenital nephrotic syndrome in a neonate. *Arch Dis Child* 1990; 65:992–3.
2 Seppala M, Rapola J, Huttunen N-P, Aula P, Karjalainen O, Ruoslahti E. Congenital nephrotic syndrome: prenatal diagnosis and genetic counselling by estimation of amniotic-fluid and maternal serum alpha-fetoprotein. *Lancet* 1976;ii:123–4.
3 Aula P, Rapola J, Karjalainen D, Lindgren J, Hartikainen AL, Seppala M. Prenatal diagnosis of congenital nephrosis in 23 high risk families. *Am J Dis Child* 1978;132:984–7.

Retinal haemorrhages in falciparum malaria

SIR,—Kaur and Taylor, in their otherwise extensive review of retinal haemorrhages in children, omitted arguably the most common cause in the world—falciparum malaria.[1]

Retinal haemorrhages are present on admission in 6–8% of children with cerebral malaria[2 3] with haemorrhages developing in a further 4% of children after treatment (personal observation). Their incidence in uncomplicated malaria has not been established. In adults haemorrhages are associated with more severe disease, as manifest by higher parasitaemias, schizontaemia, anaemia, and increased mortality.[4]

The haemorrhages are often multiple and bilateral. Most are intraretinal, either flame shaped or dot and blot, often developing white centres (Roth's spots) with time. Some are subretinal.[4]

The pathogenesis of the haemorrhages is undetermined. Although they are associated with the development of anaemia in adults with cerebral malaria they are present early in the disease when haemoglobin concentration is relatively high. Intracranial hypertension has been documented in children with cerebral malaria,[2] but there was no correlation between opening lumbar puncture pressure and haemorrhages in this study or a larger adult series.[4] Raised central venous pressure secondary to convulsions may be a cause, but haemorrhages can develop in the absence of seizures. The pathognomic histopathological feature of cerebral malaria is the sequestration of parasitised erythrocytes in small vascular beds including the retinal vessels. We have documented the appearence of haemorrhages at around the time of sequestration on several occasions. Recently it has been suggested that the phenomenon of 'rosetting' of uninfected cells around the parasitised cells plays a part in the pathogenesis of cerebral malaria,[5] and it is possible that the lodging of these agglutinates in the retinal vessels leads to haemorrhages. Haemorrhages were not associated with thrombocytopenia or disseminated coagulation in adults.[4]

Whatever the mechanism, falciparum malaria probably causes, at a conservative estimate, a quarter of a million new cases of retinal haemorrhage a year in children, and as such is worthy of a mention.

C R J C NEWTON
P A WINSTANLEY
K MARSH
Clinical Research Centre,
(Kilifi Research Unit),
PO Box 428,
Kilifi, Kenya

1 Kaur B, Taylor D. Retinal haemorrhages. *Arch Dis Child* 1990;65:1369–72.
2 Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989; 265:441–59.
3 Newton CRJC, Kirkham FJ, Winstanly PA, *et al.* Intracranial pressure in African children with cerebral malaria. *Lancet* 1991 (in press).
4 Looareesuwan S, Warrell DA, White NJ, *et al.* Retinal haemorrhage, a common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 1983;32:911–5.
5 Carlson J, Helmby H, Hill AVS, *et al.* Human cerebral malaria: association with erythrocyte rosetting and lack of antirosetting antibodies. *Lancet* 1990;336:1457–60.

Establishment of working definitions in nocturnal enuresis

SIR,—The recent paper by Dr Butler highlights the need for consistent use of nomenclature when reporting studies of nocturnal enuresis.[1] However there are several points worthy of comment. Why include only those wetting more than 50% of nights during the baseline when this will exclude many enuretics equally in need of help who he admits are 'more difficult to treat'. Furthermore, by selecting only the wettest patients from your baseline period you risk the phenomenon of 'regression towards the mean' biasing your results towards subsequent improvement irrespective of treatment.

The working definitions proposed by Dr Butler would provide only limited information on the effects of drug treatments for enuresis. The application of these definitions would satisfactorily highlight the generally low rates of 'initial arrest' of enuresis and the high subsequent relapse rate,[2] but they would fail to describe the lesser degrees of improvement that many children achieve while taking desmopressin or tricyclics. Although the gold standard for treatment is a 'cure', many fail to achieve this with conditioning therapy and for these children the temporary improvement that drugs may effect, such as an increase in the number of dry nights or a reduction in the size of the 'wet patch', are perceived as worth while.

It is important that these benefits are not overlooked when considering drug treatments for nocturnal enuresis.

J H C EVANS
Department of Paediatrics
and Child Health,
St James's University Hospital,
Leeds LS9 7TF

1 Butler RJ. Establishment of working definitions in nocturnal enuresis. *Arch Dis Child* 1991;66: 267–71.
2 Meadow SR, Evans JHC. Desmopressin for enuresis. *BMJ* 1989;298:1596–7.

Dr Butler comments:

Dr Evans's comments regarding my article on working definitions in nocturnal enuresis[1] raise some interesting issues, which are predominantly concerned with the model's applicability to groups of children (for example, those who have infrequent bedwetting accidents) and methods of treatment (for example, medication) not originally the prime focus of the initial survey.

In an attempt to establish some consistent definitions of nocturnal enuresis, which Dr Evans agrees are badly needed, I embarked on a survey of published reports of conditioning methods, given that these can be regarded as 'easily the most successful specific treatment available'.[2] The method of arriving at the proposed definitions is contained within the article and they were discussed at length at the National Enuresis Research Steering Group, the body which orginally invited me to pursue this work. The suggested baseline inclusion criteria of '50% or more wet nights in a two week period' was offered as a means of encouraging homogeneity of samples in future studies of treatment effectiveness. My intention was clearly not to detract from studies of children who wet infrequently, who as Dr Evans suggests are a very interesting and deserving population. Rather I am concerned that where such a population are studied, for reasons of clarity, the authors might be encouraged to state the degree of severity of wetting. Indeed, I believe the article stated as much.

I would argue that the proposed definitions of initial success, drop out, relapse, etc, although derived from studies on conditioning methods, are equally applicable to assessing the effectiveness of other interventions be they medication, diet, hypnosis or whatever, as they outline, reasonably unambiguously, the criteria to be met.

Dr Evans stresses the absence of measures of improvement for those children who failed to meet the initial success criteria. I would agree that monitoring of progress is essential, whatever the treatment interventions, and indeed measures of improvement such as size of wet patch, time of accident, and so on have been outlined in detail elsewhere.[3] Given such measures, however, the objective either in clinical terms or research methodology must remain the achievement of an initial success criteria.

Dr Evan's final point regarding the probability of regression to the mean is clearly one variable, among many others, that would be controlled for within an appropriate experimental design. However as the regression to mean phenomena tends to describe changes on improvement measures rather than explain complete remission, it further emphasises the importance of establishing criteria for initial success as advocated in the article.

1 Butler RJ. Establishment of working definitions in nocturnal enuresis. *Arch Dis Child* 1991;66: 267–71:
2 Meadow R. How to use buzzer alarms to cure bed-wetting. *BMJ* 1977;ii:1073–5.
3 Butler RJ. *Nocturnal enuresis: psychological perspectives*. Bristol: Wright, 1987.

SISTER JOURNALS—UNITED STATES

Pediatrics

Each issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), is sufficiently weighty as to perhaps deter the casual reader. Overcoming this feeling and investigating further, despite the excellent scientific content, one is not altogether reassured to find that almost 30% of the pages are given over to commercial advertising, mainly pharmaceuticals. I suppose this reduces the costs to subscribers, but I find it worrying to see in one issue 12 pages devoted to antitussives, antipyretics, and decongestants, together with adverts for products of dubious utility such as an adsorbent for treating acute diarrhoea, fructose/dextrose mixture for nausea, and carnitine for '. . the lethargic, hypotonic child; the fretful infant who doesn't eat; no specific evidence of disease. . . yet something clearly is wrong'. Although there is a disclaimer to the effect that publication of an advertisement does not imply endorsement by *Pediatrics* or the AAP, I can't help feeling that the volume and content of the promotional material somehow detract from the primary aims of the journal to inform and educate its readers.

If this tells us something about the relationship between the medical profession and the drug industry in the United States, the generally high standard of the papers and their wide ranging subject matter tell us more about the fostering of high quality scientific research there. Many different areas of paediatric care are covered and there is much to interest UK paediatricians. In addition, some intriguing insights into health care and society in North America are offered, for example the hospital in the Bronx which sees 60 000 children a year in its paediatric casualty department, 95% of whom are Hispanic, African-American, or Asian. To inform and educate patients waiting their turn to see the doctor, there are companies vying with each other to supply a television in the waiting room exclusively showing health education programmes. However, too much television can be bad for you, and perhaps explains the reported finding that only 42% of American 17 year olds can read well enough to understand an editorial in a major newspaper.

Not surprisingly some areas of professional concern are common to both the UK and the United States. Accident prevention is given a laudably high profile and in this issue of *Pediatrics* the AAP policy statement on safe transportation of newborns discharged from hospital is reproduced. Parents may also buy a video film featuring a well known actress discussing car safety, and management of choking, drowning, poisoning, cuts, burns, and head injuries in children. Perhaps we in the UK should explore video film as a means of disseminating popular health information. The policy statements of the AAP are published regularly in the journal and I wonder if similar space in the *Archives of Disease in Childhood* could not be given to the British Paediatric Association?

J W L PUNTIS

Polymerase chain reaction in the diagnosis of tuberculous meningitis

New methods of diagnosing tuberculous meningitis appear to be proliferating. Last year Lu and coworkers in Shanghai and Stockholm described the use of a nitrocellulose enzyme linked immunospot assay for detecting cells in blood or cerebrospinal fluid which are secreting antigen specific IgG or IgA antibodies (see Archivist, October 1990:1192). They mentioned the possibility of using the polymerase chain reaction (PCR) as a further method aiming at early rapid diagnosis. Now researchers in New Delhi have published their experience with PCR (Shankar *et al*, *Lancet* 1991;337:5–7).

They found positive results on examining the cerebrospinal fluid in 75% (15 of 20) of cases of 'highly probable' tuberculous meningitis. Unfortunately on first testing the method gave positive results in 14% of cases of pyogenic meningitis. On repeating the tests on saved samples, however, they got negative results. They explain the initial positive results on the basis of sample contamination and claim that 100% specificity should be achievable.

The test used by Lu *et al* was positive in 96% of cases (24 of 25) and one of 12 controls. A direct comparison of the two tests on the same patients seems indicated. They both seem to be much superior to conventional methods of diagnosis and may save many lives by allowing earlier diagnosis and treatment.

ARCHIVIST

Equipment requirements for community based paediatric oxygen treatment

Cheryl Angell

Equipment	*Reason for choice*	*Decision maker on equipment*	*Who provides equipment*	*Who covers cost of equipment*	*Comments*
(1) Domiciliary systems:					
(A) Oxygen concentrator with low flow meter attachment	Best option when a continuous supply of oxygen is required. Less stressful for parents and more economical. To contact concentrator contractors dial 100 and ask for Freephone Oxygen	Hospital consultant	Concentrator provided by contractors—for example, DeVilbiss and Omnicare Low flow meter by contractor: *DeVilbiss*—charge £150 and sell equipment to the hospital. *Omnicare*—£40 rental charge to the hospital for as long as client requires equipment. *By hospital itself*—for example, Platon flow meter and technicians time to make a suitable bracket for fitting to the machine £90–120 approximately	FHSA Low flow meter: referring hospital—for example paediatric budget	A concentrator is preferable for the provision of long term oxygen treatment for paediatrics. Family also benefit from the companies maintenance support. At present, the hospital meets the expense of the low flow meter. It would be preferable if it was included in the concentrator package and funded by the FHSA
(B) Oxygen cylinders with bullnose regulator and low flow meter	When oxygen is used infrequently—for example, symptomatic relief	Hospital consultant	Cylinders: general practitioner on prescription (size F). Regulator and low flow meter. are provided by the hospital	Cylinders by FHSA Regulator and low flow meter paid for by hospital: £51·50 for bullnose regulator, £40 low flow meter approximately	Less likely treatment choice. Majority of patients go home on low flows on continuous supply
(2) Portable systems:	Portables are essential to avoid mother and child becoming housebound	Hospital consultant (choice of equipment depends on its availability)	All portable systems are provided for by the hospital. Nothing is available on prescription	Hospital covers all the portable system costs	
(A) Hospital 'C' or 'D' cylinder: pin index regulator, low flow meter				Pin index regulator £69·15, low flow meter £40	Cumbersome system. Exchange of empty for full oxygen cylinders at hospital pharmacies causes practical problems. Sometimes not negotiable
(B) Sabre AAV low flow oxygen treatment equipment. Tel No 0252 334581				Sabre AAV: microcontroller £23·65, flow indicator £9·90, oxygen portable multiflow bullnose 1, 1·5, 2, 2·5, 3, 125L=£165·05, 230L=£171·95, recharging adaptor =£33·50; settings at lower flows available on request	Most preferable system as refillable from domiciliary oyxgen cylinders at home

FHSA, Family Health Services Authority.

Department of Occupational Therapy, Royal Brompton and National Heart Hospital, Sydney Street, London SW3 6NP
Cheryl Angell

Inquiries to:
Ms Cheryl Angell or
to Dr Martin Samuels,
Dr David Southall,
Sister K Jones or
Sister J Noyes in the
Department of Paediatrics
at the Royal Brompton and
National Heart Hospital.

INSTRUCTIONS TO AUTHORS

Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Submission of a paper will be held to imply that it contains original work not being offered elsewhere or published previously. Manuscripts should be prepared in accordance with the Vancouver style.[1] The Editors retain the right to shorten the article or make changes to conform with style and to improve clarity.

For guidance on ethical aspects refer to the editorial in this journal.[2] All authors must sign the copyright form after acceptance.

Failure to adhere to any of these instructions may result in delay in processing the manuscript and it may be returned to the authors for correction before being submitted to a referee.

General

- Authors must submit two copies of the manuscript and any subsequent revision.
- When submitting original manuscripts authors should send a copy of any of their other papers on a similar subject to assure the editors that there is no risk of duplicate publication.
- Manuscripts must have a title page which gives the title of the paper, the name of the author(s), the place where the work was carried out, and the address of the corresponding author. The authors should include their family names and initials. The number of authors should be kept to a minimum and should include only those who have made a contribution to the research: justification should be made for more than five authors. Acknowledgments should be limited to workers whose courtesy or assistance has extended beyond their paid work, and to supporting organisations. Information about the availability of reprints should be given at the end of the references.
- The article and references must be typed in double line spacing throughout (including tables) with a 5 cm margin on the left side. The right hand margin should not be justified. Pages should be numbered in the top right hand corner.
- All measurements must be in SI units apart from blood pressure measurements, which should be in mm Hg and drugs in metric units.
- Abbreviations should be used rarely and should be preceded by the words in full before the first appearance.
- In the statistical analysis of data 95% confidence intervals should be used where appropriate.
- Any article may be submitted to outside peer review and for statistical assessment. This may take up to six weeks. Articles are usually published within five months of the date of the final acceptance of the manuscript.
- No free reprints will be provided. Reprints may be ordered when the proof is returned; they take about two months to be dispatched and those going overseas are sent by surface mail.
- If the paper is rejected the manuscript and all illustrations will be shredded unless a request is made at the time of submission for return of the illustrations.

Original articles

- The title should have no more than 10 words and should not include the words 'child', 'children', or 'childhood' (already implicit in the title of the journal).
- The abstract of an experimental or observational study must clearly state in sequence and in not more than 150 words (i) the main purpose of the study, (ii) the essential elements of the design of the study, (iii) the most important results illustrated by numerical data but not p values, and (iv) the implications and relevance of the results. The abstract of a paper which focuses on a case report(s) must summarise the essential descriptive elements of the case(s) and indicate their relevance and importance.

Short reports

- Length must not exceed 900 words, including an abstract of less than 50 words, one or two small tables or illustrations and up to six references. If more illustrations are required the text must be reduced accordingly.
- The title should be no longer than seven words.

Annotations

- Annotations are commissioned by the editors who welcome suggestions for topics or authors.

Letters

- Letters must be typed in double line spacing, should normally be no more than 300 words, have no more than four references, and must be signed by all authors. Two copies should be provided. Letters may be published in a shortened form at the discretion of the Editor.

Tables and illustrations

Tables should be submitted separately and typed in double line spacing without ruled lines.

- Avoid histograms if possible.
- Illustrations should be used only when data cannot be expressed clearly in any other way. When graphs are submitted the numerical data on which they are based should be supplied.
- Illustrations should be trimmed to remove all redundant areas; the top should be marked on the back.
- Patients shown in photographs should have their identity concealed or written consent to publication should be obtained.
- Ultrasound scans or other pictures should be arrowed on an overlay to indicate areas of interest or should be accompanied by explanatory line drawings.
- If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder (usually the publisher) and the authors. A copy of the letter giving consent must be included.

References

- References must be numbered in the order they appear in the text and include all information (Vancouver style):

  1 Williams W, Sunderland R. As sick as a pigeon—psittacosis myelitis. *Arch Dis Child* 1989;**64**:1626–8.
  2 Hughes CA. Parenteral nutrition. In: Insley J, Wood B, eds. *A paediatric vade mecum*. London: Lloyd-Luke, 1984:60–7.

- Please note that in the new Vancouver style (4th edition, 1991) all authors must be given but if the number exceeds six give six names followed by *et al* (instead of three).
- Abstracts, information from manuscripts not yet accepted, or personal communications may be cited only in the text and not included in the references. References are not checked by us; authors must verify references against the original documents before submitting the article.

1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1988;**296**:401–50.
2 Anonymous. Research involving children—ethics, the law, and the climate of opinion. [Editorial.] *Arch Dis Child* 1978;53: 441–2.

Manuscript checklist:

- Is the entire manuscript double spaced?
- Is there an abstract?
- Are the references in Vancouver style?
- Are the abbreviations spelt out?
- Are the measurements in SI units?

Revised June 1991

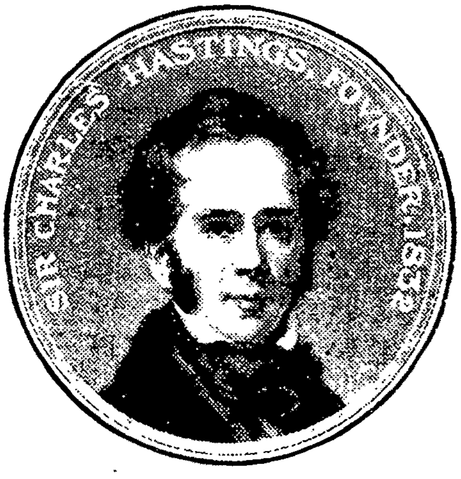
SPECIAL BMA MEMBERS EDITION

MIRROR OF MEDICINE

A HISTORY OF THE BMJ

P. W. J. BARTRIP

THE BRITISH MEDICAL ASSOCIATION
MDCCCXXXII



BMJ
1840-1990

The *BMJ*'s 150 year history has taken it from small beginnings in Worcester as the *Provincial Medical and Surgical Journal* to its current position as a major international medical journal. On the way there have been rows, editors' dismissals, and battles with the BMA and royal colleges as well as growing success and authority. In *Mirror of Medicine* the historian P W J Bartrip provides a shrewd and perceptive commentary on the *BMJ*'s progress, placing its history in the context of contemporary events and examining its treatment of many key themes in medical science and society, including public health, military medicine, quackery, sex, and the birth of the NHS. He also provides pen portraits of some of its most outstanding editors, among them the charismatic Ernest Hart, his successor Dawson Williams, and the doughty Hugh Clegg. The *BMJ*'s present editor, Stephen Lock, provides a postscript on the state of the *BMJ* today.

352 pp., illus., Clarendon Press/BMJ, September 1990

Price to BMA members only: UK £29; Abroad £33. Prices include packing and postage, by air speeded despatch abroad (air mail rates on application). American Express, Mastercard, Visa credit cards accepted. Please give full details.

Return address for orders: British Medical Journal, PO Box 295, London WC1H 9TE. (Also available in the BMJ/BMA bookshop in BMA House.)

Calculate with confidence

CIA software

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton. The program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- non-parametric analyses

For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program may also be used in conjunction with the book *Statistics with Confidence*, which provides numerous worked examples. The software is available for IBM compatibles on either a 5¼″ or a 3½″ disk.

Price: £65.00. Educational establishments, research institutes, and the NHS — £45.95. Prices include VAT in the UK and air mail despatch abroad.

The book *Statistics with Confidence – Confidence intervals and statistical guidelines* is available price £7.95 in the UK and £9.50 abroad (BMA members £7.45 and £9.00, respectively)

ORDER FORM BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE, England

Please send me .... copy/copies of *Confidence Interval Analysis (CIA)* at £65.00 (full price) or £45.95 (educational establishments, research institutes, and the NHS).

Size of disk required ☐ 5¼″ disk ☐ 3½″ disk *(please tick relevant box)*

Please send me .... copy/copies of *Statistics with Confidence – Confidence intervals and statistical guidelines* at UK £7.95 and abroad £9.50 (BMA members £7.45 and £9.00 respectively)

I enclose .... *(please make cheques payable to* **British Medical Journal**) or debit my credit card

☐ American Express ☐ Mastercard ☐ Visa Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Card Expiry Date .... Signature ....

BMA Membership No. (where applicable) ....

NAME (BLOCK LETTERS PLEASE) ....

ADDRESS ....

....

.... POSTAL CODE ....

BRITISH PAEDIATRIC ASSOCIATION

ALLEN & HANBURYS RESEARCH AWARD

[redacted]

“Days

[redacted]

FETAL AND NEONATAL EDITION

UCM

JULY 1991 VOL 66 NO 7

11/
Dec. 12 92

[redacted]

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Editors: Bernard Valman, Malcolm Chiswick
Associate Editors: Derek Johnston, Michael Silverman, Brian Wharton
Statistical Adviser: Michael Healy
Technical Editor: Mary Evans
Editorial Assistant: Jacinta Marshall

EDITORIAL COMMITTEE

F Cockburn
T J David
M J Dillon
M E Garralda
H L Halliday
I M Hann
I A Hughes
J W Keeling
C R Kennedy
S W Lenton
J K Lloyd
H Marcovitch
N McIntosh
P J Milla
L Polnay
P Raine
P T Rudd
J F N Taylor
R M Winter
J E Wraith
Editor, *BMJ*

Published by the British Medical Association, Tavistock Square, London WC1H 9JR and printed in England by The Devonshire Press Ltd, Torquay.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NH 07001, USA.

ISSN 0003–9888

NOTES TO CONTRIBUTORS Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

NOTICE TO ADVERTISERS Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *Archives of Disease in Childhood* is published monthly. The annual subscription rates are £127 inland and £140 overseas (USA $208). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All inquiries however must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

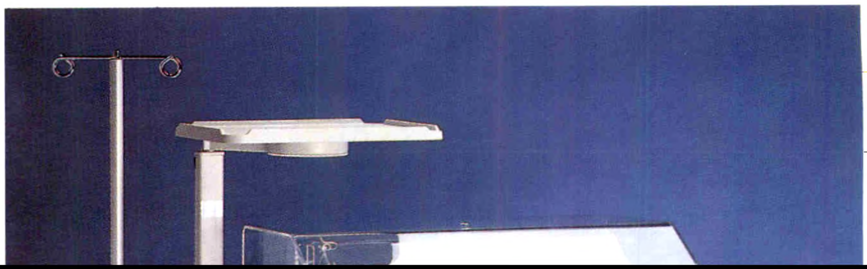
All inquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

COPYRIGHT © 1991 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Some infants are ahead of their time.

[redacted]

The loudest noise in your S.C.B.U. should be the sound of babies sleeping



But how often have you walked into the Special Care Baby Unit only to be greeted by a wall of noise?

We all know babies nursed in incubators need rest — indeed most of them should still be in the calm of the womb.

[redacted]

Archives of Disease in Childhood 1991; **66:** 757–764

ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

ORIGINAL ARTICLES

Cost implications of different approaches to the prevention of respiratory distress syndrome

Miranda Mugford, James Piercy, Iain Chalmers

National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE
Miranda Mugford
James Piercy
Iain Chalmers

Correspondence to:
Mrs Mugford.

Accepted 18 January 1991

Abstract

Because the incidence of both neonatal respiratory distress syndrome and neonatal mortality can be reduced by giving corticosteroids to women expected to deliver preterm and by giving surfactant to babies at high risk of developing hyaline membrane disease, we have considered what effects the adoption of one or both of these preventive policies would have on the costs of neonatal care. We have estimated the effects of treatment from overviews of the relevant controlled trials, and estimated costs from observations of care at one neonatal unit. Our results suggest that if either of these policies is adopted for all babies under 35 weeks' gestation at a drug cost of £150 or less/baby, the overall costs of care would be reduced by between 1 and 10%. The cost per survivor would be reduced by up to 16% even if the drug cost were to be as high as £550/baby. If the policies were to be adopted only for babies under 31 weeks' gestation, both policies would result in a reduction in cost of between 5 and 16%/survivor, although the increased survival resulting from the policies would lead to an increase in overall costs for babies of less then 31 weeks' gestation of between 7 and 32%.

Although neonatal intensive care is more cost effective than many other widely accepted components of health care,[1] it is one of the most costly parts of the perinatal health services.[2–13] The costs of caring for babies who require artificial ventilation are particularly high,[3,13] and a high proportion of these babies have respiratory distress syndrome. Interventions that reduce the incidence of respiratory distress syndrome are clearly desirable because they reduce morbidity and mortality. In addition, however, they may reduce the costs of neonatal intensive care both for the health services and for those using them.

There is now strong evidence that the incidence of respiratory distress syndrome can be reduced by at least two prophylactic policies: giving corticosteroids to women who are expected to deliver preterm, and giving surfactant to babies judged to be at high risk of developing respiratory distress syndrome. We are not the first to draw attention to the potential economic benefits of these forms of prophylaxis. The potential cost saving from using antenatal corticosteroids was noted in a leading article in the *Journal of Pediatrics* in 1984,[14] and it was estimated in one of the controlled trials of antenatal corticosteroids that prophylaxis had more than halved subsequent hospital charges in the group that had received the drugs.[15] The economic consequences of adopting early treatment with surfactant are less certain, because it is clear that the market cost of surfactant will be considerable. Although some of the available estimates suggest that savings are unlikely to be as dramatic as with antenatal corticosteroids,[16] giving surfactant early to immature infants may nevertheless be cost effective.[17]

In this paper we present estimates of the likely effects of introducing each of these prophylactic strategies on health service costs.

Materials and methods

Our aims were to derive estimates from overviews of controlled trials of the effects of the two policies on respiratory distress syndrome and mortality; to observe the costs of care for preterm babies in a unit where mothers did not (at the time of the study) routinely receive steroids as a prophylactic measure against respiratory distress syndrome, and where babies were not given surfactant; and, using these two sources of data, to predict the expected effect on costs of introducing different policies for prevention of respiratory distress syndrome in that unit.

ASSESSMENT OF EFFECTS OF INTERVENTIONS TO REDUCE THE INCIDENCE OF RESPIRATORY DISTRESS SYNDROME

Prenatal administration of corticosteroids

Estimates of the effects of corticosteroids on the incidence of respiratory distress syndrome and early neonatal death were derived from an analysis of 12 trials of prenatal corticosteroids incorporated in the overview reported by Crowley and her colleagues.[18] These trials together included a total of 3266 babies judged prenatally to have been at increased risk of developing respiratory distress syndrome. Although the entry criteria for these trials differed in some details, most of the babies studied were between 24 and 34 weeks' gestational age at birth.

Early postnatal administration of surfactant

Estimates of the effects of prophylactic surfactant were derived from overviews reported by Soll.[19 20] The trials included babies of between 24 and 34 weeks' gestation (or who were in equivalent birthweight categories). The estimate of the effect of surfactant on the incidence of respiratory distress syndrome was based on data derived from the 1491 babies who participated in the 10 trials in which this outcome was reported. The estimate of the effect on the risk of death before discharge from hospital was based on data derived from 1924 babies who participated in a total of 14 trials.

The methods used in creating the overviews have been described more fully elsewhere.[21] Estimates of the effects of the two interventions were derived using a modification of the Mantel-Haenszel method,[22] and have been expressed as summary odds ratios with their 95% confidence intervals (CI).

ESTIMATION OF COSTS

Our costing study was carried out at the neonatal unit of the John Radcliffe Maternity Hospital, Oxford. The aim of this part of the study was to estimate the difference in costs of neonatal care for babies with and without respiratory distress syndrome who survived to be discharged, and also for those who died. These costs were estimated for babies admitted to the unit during the first half of 1989. The criteria for diagnosing respiratory distress syndrome were as follows: tachypnoea (more than 60 breaths/minute), substernal and intercostal recession; grunting, disease increasing in severity over 24–36 hours, and clinical diagnosis supported by radiological appearances.

To estimate the costs of treating respiratory distress syndrome, we estimated the cost at each of the levels of care from detailed review of the treatment of eight babies admitted during the period with a range of gestational ages. Four of these babies, with gestational ages of 28, 32, 34, and 36 weeks, met the diagnostic criteria for respiratory distress syndrome. We then selected the casenotes of four control babies, who were discharged from hospital at about the same time, but who had not developed respiratory distress syndrome and were as close in gestational age as we could find (30, 30, 32, and 36 weeks).

Procedures noted in the case records were costed by observation of care in the neonatal unit. One of us (JP) made detailed observations of the staffing, equipment, and clinical procedures used in the care of newborns in the unit during the two months of July and August 1989. We obtained administrative data about the costs of services provided to the neonatal unit by the pharmacy, and by the departments of pathology, radiology, and physiotherapy. Overhead costs were for ward overheads, and did not include any element for capital value of the building. Details of the costing methods are given elsewhere.[23] From these data we used simple algebra to calculate average costs/day of care for three levels of care experienced by the eight babies in the detailed study: babies having intermittent positive pressure ventilation (IPPV), babies given oxygen without IPPV, and babies receiving other special care.

The expected cost of care for the 70 babies with gestational ages of less than 35 weeks admitted to the unit between 1 January and 30 June 1989 were calculated from data about the average length of stay at each of these levels of care, together with cost data from our observations about the costs of different levels of care. These costs were tabulated by diagnosis of respiratory distress syndrome, by whether the baby survived to be discharged or not, and by gestational age. To avoid the problem of measuring the use of resources in more than one hospital, we studied only babies born within the John Radcliffe Maternity Hospital and not transferred elsewhere.

The costs of steroids and surfactant were estimated after discussion with pharmacists and clinical staff. Giving steroids is likely to add relatively little to the cost of care, as a woman admitted to hospital with threatened preterm delivery is likely to receive a high level of obstetric and midwifery care whether or not she is given these drugs, thus the marginal cost is likely to be the cost of the drug and the materials needed to give it. The additional cost of giving surfactant to infants at high risk of developing respiratory distress syndrome is also likely to be low, because it is likely that continuous paediatric medical care would anyway be required at this stage in the life of these babies. The drug cost/dose is considerably higher than that for corticosteroids. For this study we calculated expected costs based on high and low estimates of its cost.

All estimates of financial costs have been based on 1989 prices. The estimated value of capital equipment used was calculated using the method now recommended for NHS accounts, using straight line depreciation over seven years, with an added annual fixed interest charge of 6%.

ESTIMATING THE LIKELY IMPACT OF INTRODUCING MEASURES TO PREVENT RESPIRATORY DISTRESS SYNDROME AT THE JOHN RADCLIFFE MATERNITY HOSPITAL

Data were collected from routine sources about all the babies of less than 35 weeks' gestation who were born between 1 January and 30 June 1989 and admitted to the neonatal unit. These provided information about whether babies had developed respiratory distress syndrome, and whether they had survived to be discharged. To assess the proportion of babies that might have benefited from antenatal corticosteroids, further data about the length of time between the mothers' admission and their delivery were collected from the labour ward delivery book.

To assess the likely impact of adopting each of these prophylactic strategies on the incidence of respiratory distress syndrome and death in this cohort, we calculated expected numbers by applying the typical odds ratios derived from the trial overviews to the observed odds of occurrence of the two outcomes, using the formula:

$$R_e = \frac{NR_oT/(N-R_o)}{1+[R_oT/(N-R_o)]}$$

Where: R_e=expected number with particular outcome with prophylactic intervention; N= total number of babies; R_o=observed number of babies with particular outcome without the prophylactic intervention; and T=typical odds ratio for the effect of the prophylactic intervention.

Results

EFFECTIVENESS OF PROPHYLACTIC CORTICOSTEROIDS AND SURFACTANT

Table 1 shows typical odds ratios and 95% CI for the effects of prenatal corticosteroids and early postnatal surfactant on respiratory distress syndrome and on mortality. The 95% CI for the typical odds ratio (the ratio between the odds for the intervention and control populations) for antenatal corticosteroid administation is between 0·41 and 0·60, which means that the prophylaxis is likely to reduce the odds of respiratory distress syndrome by between about 60 and 40%. The reduction in the odds of respiratory distress syndrome likely to follow early administration of surfactant lies between about 50 and 25%, because the confidence interval for the typical odds ratio is between 0·49 and 0·75. Both prophylactic regimens are also associated with a significant and clinically important reduction in the risk of death. The available data on longer term effects are reassuring for corticosteroids but not yet available for surfactant.[18]

Table 1 Effect of prophylaxis with antenatal corticosteroids and early surfactant administration on respiratory distress syndrome and mortality

	No of trials	*No of babies*	*Typical odds ratio*	*95% CI*
Antenatal corticosteroids:[18]				
Respiratory distress syndrome	12	3266	0·49	0·41 to 0·60
Early neonatal death	12	3266	0·59	0·47 to 0·75
Early postnatal surfactant administration:[19 20]				
Respiratory distress syndrome	10	1491	0·61	0·49 to 0·75
Death before discharge	14	1924	0·55	0·43 to 0·70

COSTS OF RESPIRATORY DISTRESS SYNDROME

The detailed costs of caring for babies with and without respiratory distress syndrome with comparable gestational ages are shown in table 2. The mean cost of caring for the four babies with respiratory distress syndrome (£6554/baby) was about twice that for the four controls with similar gestational ages who did not develop respiratory distress syndrome (£3265/baby). A breakdown of the costs shows that the largest absolute difference in costs is for nursing and equipment costs. Although they accounted for a smaller part of the total costs, however, relative differences in costs were greatest for biochemistry, radiology, oxygen, and pharmacy.

From these data we estimated the costs/day of care at each of the three prespecified levels of care to be as follows: with IPPV, £272; with oxygen but no IPPV, £118; and for other care in the unit, £102. Based on these costs, table 3 shows, for the 70 babies included in our study, the costs by gestational age group, survival to discharge, and diagnosis of respiratory distress syndrome. Whether or not they had respiratory distress syndrome, babies who died had received intensive care throughout their stay in the neonatal unit. Table 3 shows that the average cost of care for surviving babies under 31

Table 2 Differences in detailed cost (£ sterling) of care for four babies with and four without respiratory distress syndrome matched for gestational age

	Mean cost/case at 1989 prices		*Ratio of costs of care for those with respiratory distress syndrome:those without*
	Babies with respiratory distress syndrome	*Babies without respiratory distress syndrome matched for gestational age*	
Staff:			
Nursing	2736·53	1608·73	1·7:1
Medical	962·39	498·24	1·9:1
Physiotherapy	32·45	24·61	1·3:1
Depreciation and running costs of equipment, including ultrasound	1172·08	560·44	2·1:1
Pathology:			
Biochemistry	227·19	46·25	4·9:1
Haematology	117·00	57·00	2·1:1
Microbiology	96·00	37·12	2·6:1
Radiology (including staff and equipment)	388·80	43·20	9·0:1
Disposable supplies	276·28	158·95	1·7:1
Oxygen	88·50	2·25	39·3:1
Pharmacy (including blood products and total parenteral nutrition)	199·65	29·20	6·8:1
Overheads (including all ancillary and support services)	250·57	191·14	1·3:1
Total cost/case	6554·00	3265·00	2·0:1

Table 3 Numbers of babies and costs of care by gestation, development of respiratory distress syndrome, and outcome*

	With respiratory distress syndrome			*Without respiratory distress syndrome*		
	Total	*Died*	*Survived*	*Total*	*Died*	*Survived*
Estimated cost per baby (£, 1989 prices)						
Gestational age (completed weeks):						
<31	6385	1844	10100	4796	0	4796
31–34	3872	0	3872	2408	2227	2418
Total <35 weeks	5667	1844	7478	2635	2227	2649
No of babies						
Gestational age (completed weeks):						
<31	20	9	11	4	0	4
31–34	8	0	8	38	2	36
Total <35 weeks	28	9	19	42	2	40

*Babies less than 35 weeks' gestation admitted to the John Radcliffe Maternity Hospital neonatal unit between 1 January and 30 June 1989.

weeks' gestation with respiratory distress syndrome was more than twice that for those who did not develop respiratory distress syndrome. For babies of 31 to 34 weeks' gestation the cost is 60% higher for those with respiratory distress syndrome.

Costs of antenatal corticosteroids are between £5 and £11/woman treated. In our calculations we have assumed the cost is £7·50. The costs of most surfactant preparations are not yet known. The costs of a course of artificial lung expanding compound (ALEC) are between £700 and £800. Another artificial surfactant preparation, 'Exosurf', has recently been given a product licence for sale in the United States and is being marketed at $450/10 ml vial (Wellcome, personal communication). Our calculations in this paper have used the two extreme values of £100 and £1000/baby treated.

IMPLICATIONS OF ADOPTING DIFFERENT STRATEGIES TO PREVENT RESPIRATORY DISTRESS SYNDROME

Of the 70 babies with a gestational age of less than 35 weeks' admitted to the neonatal unit during the first six months of 1989, 28 (40%) had a diagnosis of respiratory distress syndrome. Eleven babies died before discharge from hospital. Tables 4 and 5 show, for babies

Table 4 Numbers with different outcomes and costs of prevention of respiratory distress syndrome: babies <35 weeks' gestation

Policy	*No of babies*			*Cost of neonatal care (£)**	*Cost of prevention (£)*	*Total cost/baby*		*Total cost/survivor*	
	Survived		*Died*			*£*	*Percentage change compared with no policy*	*£*	*Percentage change compared with no policy*
	With respiratory distress syndrome	*Without respiratory distress syndrome*							
(1) No antenatal corticosteroid or surfactant	19	40	11	269 085	0	3844	0	4561	0
(2) With antenatal corticosteroids	12·8	48·7	8·5	240 985	525	3450	−10	3927	−14
(3) With prophylactic surfactant:									
(A) At £100	16	48·5	5·5	258 646	7000	3795	−1	4119	−10
(B) At £1000	16	48·5	5·5	258 646	70 000	4695	+22	5095	+12
(4) Antenatal corticosteroids and surfactant for those delivered within 6 hours of mother's admission:									
(A) At £100	12·4	50·6	7	240 157	1870	3458	−10	3842	−16
(B) At £1000	12·4	50·6	7	240 157	16 594	3668	−5	4075	−10

*Excludes cost of any preventive treatment (corticosteroid or surfactant).

Table 5 Numbers with different outcomes and costs of prevention of respiratory distress syndrome: babies <31 weeks' gestation

Policy	*No of babies*			*Cost of neonatal care (£)**	*Cost of prevention (£)*	*Total cost/baby*		*Total cost/survivor*	
	Survived		*Died*			*£*	*Percentage change compared with no policy*	*£*	*Percentage change compared with no policy*
	With respiratory distress syndrome	*Without respiratory distress syndrome*							
(1) No antenatal corticosteroid or surfactant	11	4	9	146 880	0	6120	0	9792	0
(2) With antenatal corticosteroids	11·4	6·2	6·4	156 841	180	6542	+7	8912	−9
(3) With prophylactic surfactant:									
(A) At £100	12·1	8·9	3	170 426	2400	7201	+18	8230	−16
(B) At £1000	12·1	8·9	3	170 426	24 000	8101	+32	9258	−5
(4) Antenatal corticosteroids and surfactant for those delivered within 6 hours of mother's admission:									
(A) At £100	11·7	6·7	5·6	160 630	880	6730	+10	8778	−10
(B) At £1000	11·7	6·7	5·6	160 630	7180	6992	−14	9120	−7

*Excludes cost of any preventive treatment (corticosteroid or surfactant).

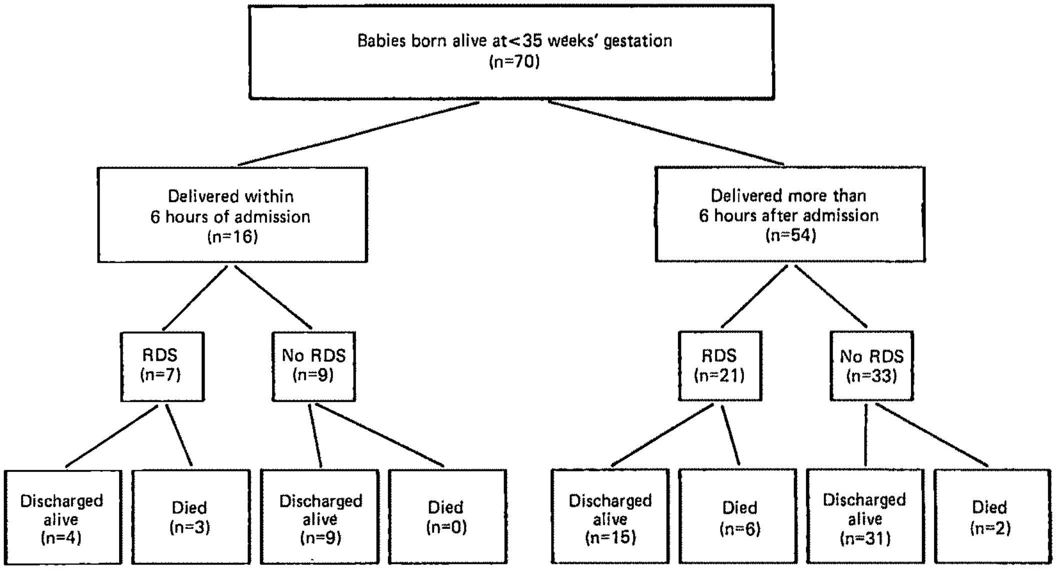


Figure 1 Observed number of babies <35 weeks' gestation with different outcomes. RDS, respiratory distress syndrome.

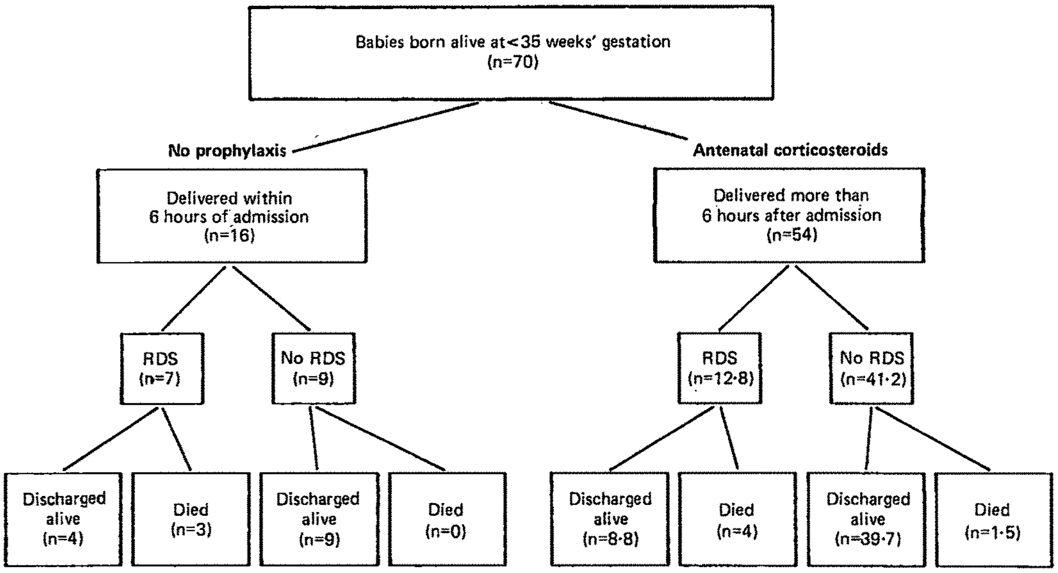

Babies born alive at<35 weeks' gestation (n=70)
No prophylaxis
Antenatal corticosteroids
Delivered within 6 hours of admission (n=16)
Delivered more than 6 hours after admission (n=54)
RDS (n=7)
No RDS (n=9)
RDS (n=12·8)
No RDS (n=41·2)
Discharged alive (n=4)
Died (n=3)
Discharged alive (n=9)
Died (n=0)
Discharged alive (n=8·8)
Died (n=4)
Discharged alive (n=39·7)
Died (n=1·5)

Figure 2 Estimated numbers of babies with different outcomes with a policy of giving antenatal corticosteroids. RDS, respiratory distress syndrome.

under 35 weeks' and under 31 weeks' gestation, respectively, the estimated costs for these 70 babies, firstly given the care that they experienced (care policy 1), and then for each of three policies for the prevention of respiratory distress syndrome (care policies 2, 3, and 4). For each policy including use of prophylactic surfactant, separate estimates are made for the upper and lower costs of surfactant.

Of the 70 babies, 16 were delivered within six hours of the mother's admission to hospital. Even if the mothers of these babies had been eligible to receive antenatal corticosteroids, we have assumed that the babies would not have benefited, but we have included the costs of giving corticosteroids to their mothers.

Figure 1 shows the observed numbers of babies with particular outcomes. Figures 2, 3, and 4 show the estimated numbers with different outcomes for three different policies of prevention of respiratory distress syndrome: firstly, use of antenatal corticosteroids for those likely to benefit; secondly, use of early prophylactic surfactant for all babies; and thirdly, use of corticosteroids for those likely to benefit,

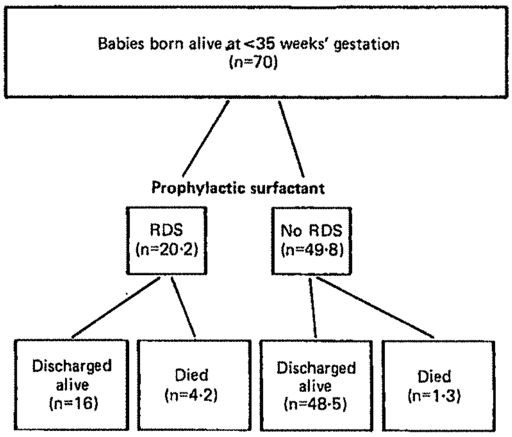


Figure 3 Estimated numbers of babies with different outcomes with a policy of early surfactant administration. RDS, respiratory distress syndrome.

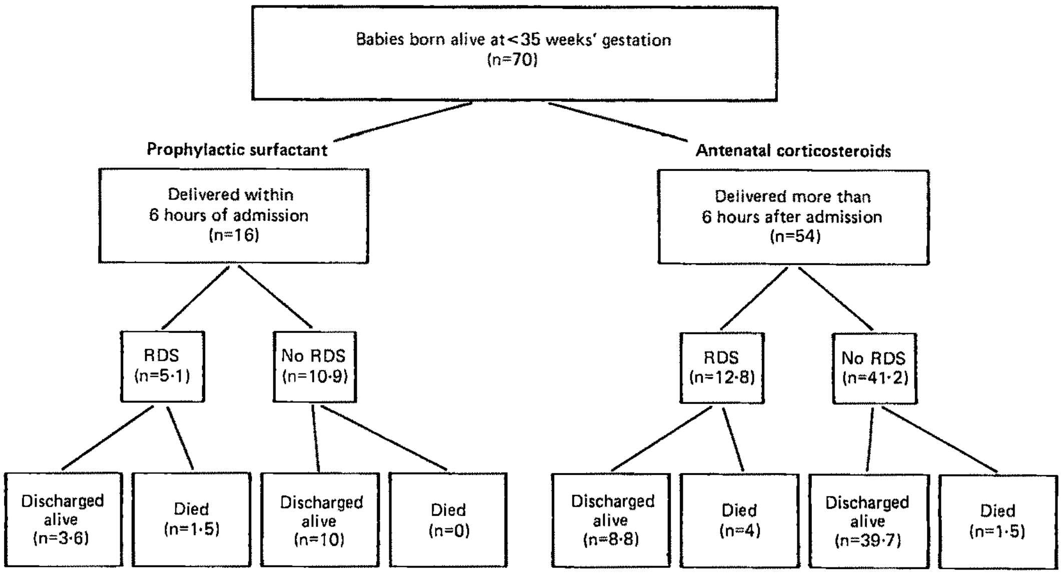


Figure 4 Estimated numbers of babies with different outcomes with a policy of giving antenatal corticosteroids combined with early surfactant administration for those babies delivered within six hours of mother's admission. RDS, respiratory distress syndrome.

together with early prophylactic surfactant for those who were unlikely to have benefited from corticosteroids. The expected costs arising from adopting each of these different policies for all babies under 35 weeks' gestation, and from adopting them only for babies under 31 weeks' gestation, are given in tables 4 and 5.

The cost of caring for the 70 babies of less than 35 weeks' gestation was estimated to have been £269 085. We estimate that the use of antenatal corticosteroids for women with gestations up to 35 weeks (policy 2 in table 4) would have reduced the number of cases of respiratory distress syndrome by 28%, and the number of deaths by 22%. Given these changes, we estimate that the costs of caring for the whole cohort of 70 babies would have been reduced from £269 085 to £240 985, which means a reduction in the average cost/baby by 10%; the cost/survivor would have been reduced from £4561 to £3927, a reduction of 14%. Applied only to mothers of babies with gestational ages of less than 31 weeks (table 5), prenatal administration of corticosteroids (policy 2 in table 5) would increase total costs by 7% because of the greater cost of caring for babies of this gestational age who would have survived, but this policy would have reduced the cost/survivor by 9%.

We estimate that early administration of surfactant to babies of less than 35 weeks' gestation (policies 3A and 3B in tables 4 and 5) would have reduced the number of cases of respiratory distress syndrome by 28%, and the number of deaths by half. The only difference between policies 3A and 3B is the cost of surfactant (costs of prevention in tables 4 and 5). The effectiveness is the same, and so the expected costs of neonatal care are the same. If the cost of surfactant were to be only £100/baby, the overall costs for the cohort of 70 babies would have decreased from £269 085 to £265 646, that is by 1%, and the cost/survivor would have been reduced from £4561 to £4119, a reduction of 10%. If the cost of surfactant were to be as much as £1000/baby, the overall costs for the cohort of 70 babies would have increased from £269 085 to £328 646—that is by 22%—and the cost/survivor would have increased by 12%. If the policy were applied only to babies of less than 31 weeks' gestation (table 5), the total cost of care would have been increased by between 18 and 32%, depending on the cost of surfactant, but the cost/survivor would have been reduced by 5%, even at the higher cost of surfactant.

If antenatal corticosteroids had been used in all the women whose babies were likely to benefit and surfactant had been restricted to the remaining babies (policies 4A and 4B in tables 4 and 5) we estimate that, in the case of gestations of up to 35 weeks, the number of cases of respiratory distress syndrome and the number of deaths would both have been reduced by 36%. Once again, the two policies (4A and 4B) differ only in the costs of surfactant. At the lower end of the range of possible costs of surfactant (policy 4A in table 5), the costs of caring for the cohort of 70 babies would have been reduced from £269 085 to £242 027, that is by 10%. The cost/survivor would have been reduced by 16%. At the higher end of the range of possible costs of surfactant (policy 4B in table 5), the costs of caring for the cohort of 70 babies would still have been reduced by 5% and the cost/survivor by 10%. Applied only to babies of under 31 weeks' gestation (table 5), this policy would have increased total costs by between 10 and 14%, but the cost/survivor would have been reduced by at least 7%.

Discussion

The data we have used to assess the effects of prophylactic corticosteroids and surfactant were derived from controlled trials involving substantial numbers of babies, so our estimates of the effects of these policies on respiratory distress syndrome and death are likely to be secure. Furthermore, the trials incorporated in the overviews were conducted in a wide range of settings and so the results are likely to be widely applicable.

Although based on small numbers of babies studied in one neonatal intensive care nursery, our estimate that the cost of caring for babies with respiratory distress syndrome is double the cost of caring for babies of similar gestational age without respiratory distress syndrome is consistent with previous estimates. A study conducted in United States found that hospital charges for babies who had had respiratory distress syndrome were more than twice those for babies who had not developed respiratory distress syndrome, a difference which was largely accounted for by the increased need for assisted ventilation for those with respiratory distress syndrome.[3] These findings are consistent with those of a recent Irish study,[14] and are reflected in differences in reimbursement used by Medicare in the United States for babies with and without respiratory complications of prematurity.[24] The costs/day that we have calculated for different levels of care are low in comparison to costs estimated by Ryan *et al* in Leeds.[10] Several factors may explain this: we excluded outborn babies, who had higher costs in the Leeds study; secondly, the Leeds study included babies having operations and our study did not; and, thirdly, the overhead costs included in our study were much lower than those in the Leeds study. Our estimated average treatment costs are comparable with more recent data from a study of very preterm babies entered into a trial of surfactant treatment in Belfast, where the average cost/case was £5888.[25] Although the absolute costs of caring for babies with respiratory distress syndrome may vary substantially among health care settings, the ratio of costs within centres for babies of comparable gestations with and without respiratory distress syndrome (about 2:1) seems not to differ widely.

The organisation of care at the neonatal unit that we studied, where babies are moved to a different part of the unit when they are weaned from the ventilator and do not need intensive care, made it relatively straightforward for us to estimate the additional costs for babies receiving ventilation. This method could not be applied in those units where all care, at whatever level, is given to the baby in the same place. To estimate costs in such circumstances would require either more intensive work study or the use of some algorithm for allocation of costs between levels of care.

We estimated that there would have been a 10% reduction in the costs of caring for babies born at less than 35 weeks' gestation if antenatal corticosteroids had been used to prevent respiratory distress syndrome. Data from the randomised trials in which resource consequences were estimated suggest that our estimate may be conservative.[15 26] In our calculations we assumed that corticosteroids would have affected only the incidence of respiratory distress syndrome, yet the available evidence suggests that the incidence of both necrotising enterocolitis and periventricular haemorrhage would also have been reduced.[19] We also assumed that the cost of treating respiratory distress syndrome was the same whether or not those babies who had respiratory distress syndrome had been given any of the possible preventive interventions. This also seems to be a conservative assumption in the light of evidence from those trials that have recorded data on severity of disease and need for ventilation.

About 3% of live births are at gestations of less than 35 weeks (S Cole, personal communication). If the costs of care and incidence of respiratory distress syndrome at this hospital are typical, the costs of care for babies of under 35 weeks' gestation born in England and Wales in 1989 would have been around £80m. If, as seems likely, antenatal corticosteroids are not widely used by British obstetricians for the prevention of respiratory distress syndrome, the potential reduction in neonatal costs could be as much as £8m in a year in England and Wales, which is more than 1% of the total amount estimated to have been spent on the maternity services.[27]

We estimate that routine early administration of surfactant to babies born before 35 weeks' gestation would result in a 4% reduction in the costs of subsequent care. A detailed analysis of hospital charges based on two consecutive trials of the prophylactic use of calf lung surfactant showed that the total cost of neonatal care, excluding the cost of surfactant, was similar for babies receiving surfactant and for those who did not.[16] The overall cost of such a policy will depend on the unit cost of surfactant. Our estimates indicate that the policy would result in overall net savings if the cost/baby of surfactant is £150 or less. Above this price there would not be overall savings, although the cost/survivor would still be reduced up to a surfactant cost/baby of £550. Our estimates suggest that restricting early administration of surfactant to babies born at less than 31 weeks' gestation would increase overall costs while reducing the cost/survivor. Analyses of data collected within a controlled trial conducted in Canada have shown that the cost of caring for babies who received surfactant were 27% lower than the cost of caring for control babies.[17] The difference in average cost/patient was estimated to have been $C10 000, which would certainly outweight the likely costs of surfactant.

Although our analyses have not assumed that there would be an additional benefit to babies of receiving both corticosteroids and surfactant, there is some evidence to suggest that this additive effect may exist.[28 29] This too, therefore, may have led us to underestimate the cost effectiveness of these policies.

Our estimates of the changes in costs arising from policies to reduce the incidence of respiratory distress syndrome were based on relatively small numbers of cases observed in a particular unit. Others may wish to apply the approach we adopted to data derived from their own units. Furthermore, it may turn out to be preferable on cost and other grounds to withhold surfactant until clear evidence has emerged that the baby concerned has begun to develop the signs of respiratory distress syndrome. A report of a recent analysis of babies who had already developed severe respiratory distress syndrome and had been entered into a randomised trial of surfactant treatment concluded that surfactant reduced the cost/survivor. Taking account of subsequent neonatal morbidity, the use of surfactant treatment was found to reduce the cost of achieving a quality adjusted life year by £710.[25] The relative merits of early surfactant prophylaxis compared with surfactant treatment of babies who have already developed respiratory distress syndrome is currently being assessed in a number of controlled trials.[30] In at least two trials the relative costs of the alternative approaches will be assessed.[31 32]

We are grateful to the staff at the John Radcliffe neonatal unit, and particularly to Caroline Pepys, Andrew Wilkinson, and Peter Hope, for their help and advice. We also thank the staff of other John Radcliffe Hospital departments who supplied us with information. The work could not have been done without the efforts of those who synthesised the results of the relevant controlled trials, particularly Patricia Crowley, Marc Keirse, and Roger Soll. We also thank Mary Ellen Avery, Henry Halliday, Allen Merritt, Charles Normand, Andrew Shennan, Alec Turnbull, and our colleagues in the National Perinatal Epidemiology Unit for their helpful comments on drafts of this paper. The paper is based on work done by James Piercy as a project for an MSc in health economics at the University of York. The National Perinatal Epidemiology Unit is funded by the Department of Health.

1 Torrance GW, Zipursky A. Cost effectiveness in antepartum Rh immunization. *Clin Perinatol* 1984;**11**:267–81.
2 Pomerance JJ, Ukrainski CT, Ukra T, Henderson DH, Nash AH, Meredith JL. Cost of living for infants weighing 1000 grams or less at birth. *Pediatrics* 1978;**61**:908–10.
3 Phibbs CS, Williams RL, Phibbs RH. Newborn risk factors and costs of neonatal intensive care. *Pediatrics* 1981;**68**: 313–21.
4 Boyle MH, Torrance GW, Sinclair JC, Horwood SP. Economic evaluation of neonatal intensive care of very low birthweight infants. *N Engl J Med* 1983;**308**:1330–7.
5 John E, Lee K, Li G. Cost of neonatal intensive care. *Aust Paediatr J* 1983;**19**:152–6.
6 Monset-Couchard M, Jaspar M, de Bethmann O, Relier J. Coût de la prise en charge initiale des enfants de poids de naissance inférieur ou égal à 1500g en 1981. *Arch Fr Pediatr* 1984;**41**:579–85.
7 Newns B, Drummond MF, Durbin GM, Culley P. Costs and outcomes in a regional neonatal intensive care unit. *Arch Dis Child* 1984;**59**:1064–7.
8 Walker DB, Feldman A, Vohr BR, Oh W. Cost-benefit analysis of neonatal intensive care for infants weighing less than 1000 grams at birth. *Pediatrics* 1984;**74**:20–5.
9 Sandhu B, Cooke RWI, Stevenson RC, Pharoah POD. Cost of neonatal intensive care for very low birthweight infants. *Lancet* 1986;**i**:600–3.
10 Ryan S, Sics A, Congdon P. Cost of neonatal care. *Arch Dis Child* 1988;**63**:303–6.
11 Marshall PB, Halls HJ, James SL, Grivell AR, Goldstein A, Berry MN. The cost of intensive and special care of the newborn. *Med J Aust* 1989;**150**:568–74.
12 Tudehope D, Lee W, Harris F, Addison C. Cost analysis of neonatal intensive and special care. *Aust Paediatr J* 1989; **25**:61–5.
13 Connolly M, Fox G, O'Connor G, Clarke T, Matthews T. Cost of neonatal intensive and special care. *Ir Med J* 1989; **89**:34–6.
14 Avery ME. The argument for prenatal administration of dexamethasone to prevent respiratory distress syndrome. *J Pediatr* 1984;**104**:240.
15 Morales WJ, Diebel D, Lazar A, Zadrozny D. The effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome in preterm gestations with premature rupture of the membranes. *Am J Obstet Gynecol* 1986;**154**:591–5.
16 Maniscalco WM, Kendig JW, Shapiro DL. Surfactant replacement therapy: impact on hospital charges for premature infants with respiratory distress syndrome. *Pediatrics* 1989;**83**:1–6.
17 Shennan A, Dunn M, Possmayer F. Cost-effectiveness of single dose surfactant prophylaxis in infants of less than 30 weeks' gestation. *Pediatr Res* 1989;**25**:231A.
18 Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1990;**97**:11–25.
19 Soll RF. Prophylactic administration of natural surfactant extract. Record No 5207. In: Chalmers I, ed. *Oxford database of perinatal trials.* Version 1.1, disk issue 3, February 1990.
20 Soll RF. Prophylactic administration of synthetic surfactant. Record No 5253. In: Chalmers I, ed. *Oxford Database of Perinatal Trials.* Version 1.1, disk issue 3, February 1990.
21 Chalmers I, Hetherington J, Elbourne D, Keirse MJNC, Enkin M. Materials and methods used in synthesising evidence to evaluate the effects of care during pregnancy and childbirth. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth.* Oxford: Oxford University Press, 1989:39–65.
22 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction, an overview of the randomised controlled trials. *Prog Cardiovasc Dis* 1985;**27**: 336–71.
23 Piercy J. A cost-effectiveness study of antenatal corticosteroids and surfactant replacement therapy in the prevention of respiratory distress syndrome in preterm infants. York: University of York, 1989. (MSc thesis.)
24 Resnick MB, Ariet M, Carter RL, *et al.* Prospective pricing system for tertiary neonatal intensive care. *Pediatrics* 1986; **78**:820–8.
25 Tubman TRJ, Normand C, Halliday H. Cost of surfactant replacement for severe neonatal respiratory distress syndrome: results of a randomised trial. *BMJ* 1990;**301**: 842–5.
26 Collaborative group on antenatal steroid therapy. Effect of antenatal steroid administration on prevention of respiratory distress syndrome. *Am J Obstet Gynecol* 1981;**141**: 276–87.
27 Comptroller and Auditor General. *National Audit Office report on the maternity services.* London: HMSO, 1990.
28 Farrell E, Silver R, Kimberlin L, Wolf E, Dusik J. Impact of antenatal dexamethasone adminstration on respiratory distress syndrome in surfactant treated infants. *Am J Obstet Gynecol* 1989;**161**:628–33.
29 Liggins GC. Obstetric and paediatric collaboration to reduce morbidity after preterm birth. *Br J Obstet Gynaecol* 1990; **97**:1–10.
30 Soll RF. Prophylactic surfactant versus treatment with surfactant. Record No 5675. In: Chalmers I, ed. *Oxford database of perinatal trials.* Version 1.2, disk issue 5, February 1991.
31 Grant A. Open study of infants at high risk of or with respiratory insufficiency: the role of surfactant (OSIRIS). Record No 5256. In: Chalmers I, ed. *Oxford database of perinatal trials.* Version 1.1, disk issue 4, August 1990.
32 Halliday H, Tarnow-Mordi WO. Fourth collaborative multicentre study of Curosurf (Curosurf 4). Record No 5677. In: Chalmers I, ed. *Oxford database of perinatal trials.* Version 1.2, disk issue 5, February 1991.

MONATSSCHRIFT KINDERHEILKUNDE

139. Band Heft 4
April 1991

Organ der
Deutschen Gesellschaft
für Kinderheilkunde

Thema des Monats

Infektionskrankheiten — diagnostische Verfahren

S. Wirth, K. M. Keller, W. Baumann, B. Zabel
Hepatitis-B-Virus-DNS. Aktuelle Diagnostik bei Kindern mit chronischer Hepatitis B 202

A. Kaufhold, E. Krug, R. Lütticken, U. Knoop, F. Bläker
Bewertung von Schnelltests zum Direktnachweis des Gruppe-A-Streptokokkenantigens in Rachenabstrichen. Untersuchung zu vier kommerziellen Testsystemen 208

Pädiatrie aktuell

Vergleich zwischen Kernspintomographie und endokrinen Störungen bei Erkrankungen des Hypothalamus-Hypophysen-Systems

Was ist die richtige Lagerung des Säuglings beim gastroösophagealen Reflux?

Für und Wider eines Neugeborenen-Screenings auf zystische Fibrose 214

Was hat das Kind?

Trainingsprogramm für die Weiterbildung zum Kinderarzt 215

Klinik und Forschung

K. Berger, D. Harms, H. Denk, J. D. Beck
Impulszytophotometrische Bestimmung des DNA-Gehaltes von paraffinfixierten Neuroblastomen 216

W. Andler
Autonome Ovarialzysten und Pseudopubertas praecox 220

K. E. v. Mühlendahl
Die Feersche Krankheit 224

Der interessante Fall

Th. Paul, A. Reimer, M. Wilken, K. Miller, H. C. Kallfelz
Komplexer zyanotischer Herzfehler bei einem Neugeborenen mit einem Cat-Eye-Syndrom 228

A. Siermann, W. Storm
Toxisches Schocksyndrom bei einem 6jährigen Jungen 231

G. Kurlemann, G. Bongartz, W. Krings, D. G. Palm
Das asymptomatische Moyamoya-Syndrom 235

H. Skopnik, P. Greven, L. Füzesi, R. Mertens, G. Heimann
Gastrointestinale Symptome bei disseminierten Langerhans-Zell-Histiozytosen. Kasuistik und Literaturübersicht 239

Wußten Sie schon?

Aus der Klinik — für die Klinik

L. Schuchmann, W. Pernice, Ch. Hufschmidt, C. P. Adler
Arthritis tuberculosa — eine seltene, aber wichtige Differentialdiagnose zur juvenilen chronischen Arthritis (JCA) 244

Was hat das Kind?

Auflösung und Kommentar des Trainingsprogramms 251

Briefe an die Redaktion — Diskussionen 248

Aus Gesellschaften und Berufsverband 251

Tagesgeschichte, Personalia 253

Tagungskalender 253

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Hong Kong Barcelona Budapest

Annual subscription: DM 298,- plus postage

European Journal of

Pediatrics

Incorporating
Acta Paediatrica Belgica
and
Helvetica Paediatrica Acta

Volume 150 No. 6 1991

The pioneers of pediatric medicine
379

Review

The treatment of minimal change nephrotic syndrome: lessons learned from multicentre co-operative studies
J. Brodehl **380**

Cardiology

Myocardial β-adrenoceptor density and the distribution of β_1- and β_2-adrenoceptor subpopulations in children with congenital heart disease
R. Kozlik, H. H. Kramer, H. Wicht, A. Krian, J. Ostermeyer, D. Reinhardt
388

Endocrinology

Determination of thyroid volume by ultrasound from the neonatal period to late adolescence
J. P. Chanoine, V. Toppet, R. Lagasse, M. Spehl, F. Delange **395**

Isolated adrenocorticotropic hormone deficiency associated with common variable immunodeficiency
P. A. Tovo, R. Lala, S. Martino, G. Pastorelli, C. De Sanctis **400**

Oral glucose tolerance testing in cystic fibrosis: correlations with clinical parameters and glycosylated haemoglobin determinations
J. De Schepper, I. Dab, M. P. Derde, H. Loeb **403**

Gastroenterology/Hepatology

What will be the adult height of coeliac patients?
E. Cacciari, G. R. Corazza, S. Salardi, M. G. Pascucci, M. Tacconi, A. Cicognani, D. Tassinari, G. Biasco, U. Volta, R. Lazzari, G. Gasbarrini
407

Dumping syndrome after combined pyloroplasty and fundoplication
K. Pittschieler **410**

Hematology/Oncology

Percentile curves for red cell indices of β°-thalassaemia heterozygotes in infancy and childhood
R. Galanello, F. Lilliu, F. Bertolino, A. Cao **413**

Detection of multidrug-resistant protein, P-glycoprotein in childhood leukaemia and lymphoma
Y. Mizuno, T. Hara, M. Nagata, A. Tawa, T. Tsuruo, K. Ueda
416

Immunology/Allergology

Griscelli disease with cerebral involvement
Á. Haraldsson, C. M. R. Weemaes, J. A. J. M. Bakkeren, R. Happle
419

Bacille Calmette-Guérin – associated neonatal hepatitis
B. Simma, O. Dietze, W. Vogel, H. Ellemunter, J. P. Guggenbichler
423

Metabolic diseases

Inadequate iron availability as a possible cause of low serum carnitine concentrations in patients with phenylketonuria
H. Böhles, K. Ullrich, W. Endres, A. W. Behbehani, U. Wendel
425

A case of abetalipoproteinaemia in a Polish family
M. Kaciński, F. Kaczmarski, W. Mieżyński, Z. Grzenda-Adamek, B. Miszczuk-Jamska, J. Stopyrowa, J. Sznajd **429**

Neonatology

Factors influencing the clinical response to surfactant replacement therapy in babies with severe respiratory distress syndrome
Collaborative European Multicentre Study Group **433**

Inflation time in mechanical ventilation of preterm neonates
M. Hird, A. Greenough **440**

Nephrology

Renal growth and function 11–28 years after treatment of Wilms' tumour
A. Mäkipernaa, O. Koskimies, J. Jääskeläinen, A.-M. Teppo, M. A. Siimes **444**

Pneumology

Unexpected side-effects of inhaled steroids: a case report
K. Priftis, M. L. Everard, A. D. Milner
448

Letters to the editors

Delayed splenic development or transient asplenia?
S. Özsoylu **450**

Reply
M. Fevzi Ozkaynak, A. Ortega **450**

Indexed in *Current Contents*

Springer International

Subscription information

Volume 150 (12 issues) will appear in 1991. Information about obtaining back volumes and microform editions available upon request.

North America. Annual subscription rate: approx. US $ 1060.00 (single issue price approx. $ 102.00), including carriage charges. Subscriptions are entered with prepayment only.

Orders should be addressed to:
Springer-Verlag New York Inc.
Service Center Secaucus
44 Hartz Way
Secaucus, NJ 07094, USA
Tel: (201) 348-4033
Telex 023125994
FAX (201) 348-4505

All other countries. Annual subscription rate: DM 1598.00 plus carriage charges; Federal Republic of Germany: DM 27.61 incl. value added tax; all other countries: DM 60.60 except for the following countries to which SAL delivery (Surface Airmail Lifted) is mandatory: Japan DM 125.40, India DM 96.60, Australia/New Zealand DM 141.00. Airmail delivery to all other countries is available upon request. Volume price: DM 1598.00, single issue price: DM 159.80 plus carriage charges. Subscriptions can either be placed via a bookdealer or sent directly to:

Springer-Verlag
Heidelberger Platz 3, 1000 Berlin 33, FRG
Tel. (0)30/8207-0, Telex 183319
FAX (0)30/8214091

Archives of Disease in Childhood 1991; **66**: 765–769

Improvement of outcome for infants of birth weight under 1000 g

The Victorian Infant Collaborative Study Group

Abstract

The two year outcome of extremely low birthweight (ELBW) infants (birth weight 500 to 999 g), born in the state of Victoria over two distinct eras, 1979–80 and 1985–7, were compared. In the 1979–80 era, 25·4% of the ELBW infants survived to 2 years of age; only 12·5% of liveborn ELBW infants survived to 2 years with no neurological disabilities. In the 1979–80 era, ELBW infants born outide the level III centres in the state were significantly disadvantaged in both mortality and neurological morbidity. By 1985–7, the two year survival rate of ELBW infants rose significantly from 25·4% to 37·9%. By 1985–7, the proportion of ELBW infants who survived to 2 years free of neurological disabilities increased from 12·5% to 26·2%. Despite the improved survival, the absolute number of 2 year old children survivors with severe neurological disabilities remained constant at 8/year in both eras. By 1985–7, fewer ELBW infants were born outside the level III centres, their survival rate remained lower, but the severe neurological disability rate in survivors was no longer significantly higher. There has been a concomitant improvement in both survival and reduction in neurological morbidity.

The Women's Royal Hospital, Melbourne
C Callanan
L W Doyle
G W Ford
E A Kelly*
W H Kitchen
A L Rickards

Newborn Emergency Transport Service, Victoria
E Bowman

The Royal Children's Hospital, Melbourne
N T Campbell
P McDougall

Monash Medical Centre, Melbourne
E A Carse
M P Charlton
J Gore
V Y H Yu

The Mercy Maternity Hospital, Melbourne
J Drew
D Heuser
E A Kelly*
A Watkins
H Woods

Victorian Perinatal Data Collection Unit, Victoria
J Lumley

Correspondence to:
Dr W H Kitchen,
Department of Obstetrics and Gynaecology,
University of Melbourne,
Parkville,
Australia 3052.

Accepted 18 January 1991

For the years 1979–80 in the state of Victoria, the survival rate of extremely low birthweight (ELBW) infants (birth weight 500 to 999 g) to 2 years of age was 25·4% (89/351); only 49·4% (44/89) of the two year survivors were free of neurological disabilities.[1] At that time, ELBW survivors born outside the level III centres had not only a lower survival rate, but also a higher rate of severe neurological disabilities than those born within the level III centres.[1]

Since 1980 perinatal care in the state has improved, the changes included increasing efforts to transfer ELBW infants in utero to one of the three level III perinatal centres for birth, additional resources for assisted ventilation in the four level III nurseries, improved resuscitation for ELBW infants born outside the level III centres, and better care during the transfer of ELBW infants after birth to the level III centres. With these changes in perinatal care in mind, it was important to determine whether the outcome for ELBW infants had improved. Hence another comparable cohort, comprising all ELBW liveborn infants in the state of Victoria during 1985–7 (inclusive), was followed up prospectively to 2 years of age, corrected for prematurity.

The aim of the present study was to compare the two year outcome of infants born during 1979–80 and 1985–7 to determine the following: (1) if the survival rate had improved, (2) whether there was any important change in the neurological impairment and disability rates in survivors, and (3) whether the infants born outside level III centres continued to be disadvantaged.

Methods

In the state of Victoria, Australia, in the years 1979–80, 351 of 115 973 (0·303%) liveborn infants were ELBW; full details of the ascertainment of ELBW infants in the years 1979–80 were obtained from multiple sources, and the results to 2 years of age have been published.[1] In the three years 1985–7 in the state, 560 of 182 719 (0·306%) liveborn infants were ELBW.[2]

For the years 1985–7 data were again obtained from multiple sources, including the Victorian Perinatal Data Collection Unit, created early in the 1980s; this unit receives basic information on all births in the state, with linkage to death certificates. The legal requirement in the state is to register all liveborn infants (with a heartbeat or any respiratory movements) irrespective of birth weight or gestational age. Data were cross checked from each of the four level III neonatal centres in the state, as well as the Newborn Emergency Transport Service.[3] The level III centres collaborated in the follow up programme of surviving children, all but one of whom had spent at least some of their hospital stay in a level III centre. The techniques of obstetric and neonatal care were similar to those described for the earlier cohort, but the increased availability of resources for intermittent positive pressure ventilation in the latter era enabled more liberal use of this technique, particularly for those infants of birth weight less than 800 g. There were no other major differences in perinatal care between the two cohorts; in particular, artificial surfactant and high frequency ventilation were unavailable.

All available children were seen at the age of 2 years, corrected for prematurity, by teams in three of the four level III centres. Some children (n=4), living in other states, were unable to attend but were examined by equivalent personnel in their home state and the results forwarded to the investigators. The children were first assessed by the psychologist, using the Bayley scales of infant development.[4] Alternative psychological tests were used occasionally, for some blind children, for children not assessed until after 30 months' corrected age, or for some children assessed in other states. The paediatrician examined the children using a standardised developmental assessment and arranged audiological and visual examinations of children who had not previously been assessed. Most members of the assessment teams, including all of the psychologists, were unaware of the neonatal course of the children, and had not been involved in their neonatal care.

The criteria for diagnosing cerebral palsy have been previously reported.[5] Disabilities caused by neurological impairments were graded into categories of decreasing severity: severe, moderate, mild, and nil. Severe disabilities comprised any of bilateral blindness, cerebral palsy in children unlikely ever to walk, and a mental developmental index on the Bayley scales 2SD or more below the mean (<69) (or 2SD or more below the mean for an alternative psychological test). Moderate disability comprised cerebral palsy in non-ambulant children who were likely to walk or sensorineural deafness requiring amplification. Mild disability comprised cerebral palsy in ambulant children, or a mental developmental index between 1SD and 2SD below the mean (69 to 84) or 1SD to 2SD below the mean of an alternative psychological test. Children who did not meet the above criteria were considered to have no disability. Children from the 1979–80 cohort had their disabilities reclassified from those previously published[1] to match the 1985–7 cohort.

Data were edited, then analysed by computer using SPSS-X package programs. Differences in proportions were contrasted by χ^2 analysis; odds ratios and 95% confidence intervals (CI) were calculated.[6] Means were compared by *t* test. To adjust for birthweight discrepancies, survival and disability rates between groups were contrasted in 100 g birthweight subgroups by Mantel-Haenszel χ^2.[7] Rates of neurological disabilities in ordered categories were compared by Mann-Whitney U test.[8]

Results

For the years 1985–7, inclusive, there were 560 liveborn infants with birth weights recorded between 500 to 999 g in the state of Victoria. Two of the livebirths were transferred from their level I hospital in the country soon after birth to a level III nursery in another state, but both died. Their outcome is included in this report. The remaining infants were all cared for within the state.

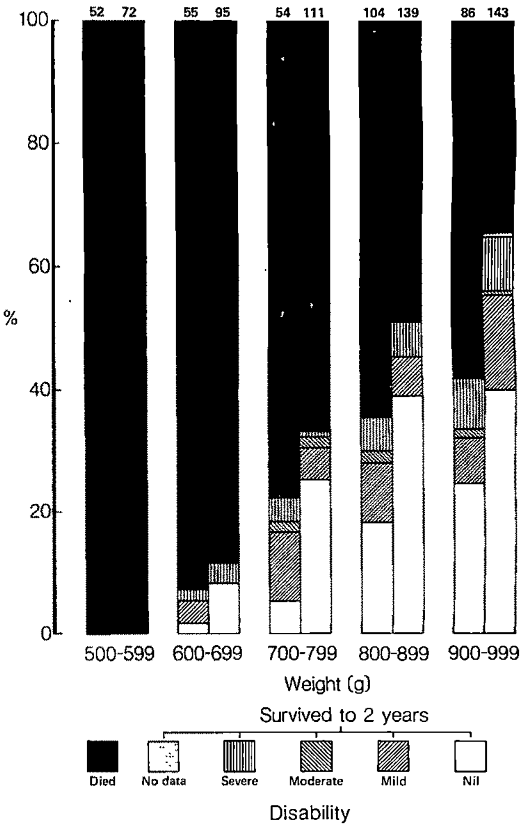
The multiple sources of data proved invaluable in identifying all known livebirths and verifying the accuracy of the data, paticularly birth weight and inhospital survival. No single source of data was error free. Up to 4% of livebirths, most of whom died, would have been missed if only one source of data had been relied upon.

Fewer ELBW infants were born outside of the level III centres in 1985–7 (23·0%, 129/560) compared with 1979–80 (30·2%, 106/351) (odds ratio 0·69, 95% CI 0·51 to 0·93, χ^2=5·4, p=0·02).

SURVIVAL TO 2 YEARS OF AGE

For 1985–7, 217 of 560 (38·7%) ELBW infants survived their primary hospitalisation; five subsequently died before the age of 2 years, three from sudden infant death syndrome. Overall, almost 50% more ELBW infants born in 1985–7 survived to 2 years' corrected age (37·9%, 212/560), compared with 1979–80 births (25·4%, 89/351) (odds ratio 1·76, 95% CI 1·32 to 2·33, χ^2=14·7, p<0·001). The survival rate rose with increasing birth weight (figure). The improved survival rate in 1985–7 was not explained by a more favourable birthweight distribution, however, as the survival rate was better within each 100 g birthweight subgroup and remained significantly higher after adjusting for birthweight (odds ratio 2·01, 95% CI 1·47 to 2·76; Mantel-Haenszel χ^2=18·3, p<0·0001).

The survival rate was higher in level III centre births compared with those born in level I or level II centres in both eras (1979–80, level III centre births 29·0%, 71/245; level I or level II centre births 17·0%, 18/106; odds ratio 1·88, 95% CI 1·12 to 3·17, χ^2=5·0, p<0·05; 1985–7, level III centre births 44·8%, 193/431; level I or level II centre births 14·7%, 19/129; odds ratio 3·6, 95% CI 2·4 to 5·4, χ^2=36·8, p<0·0001). The survival advantage for those born in the level III centres remained after adjusting for birthweight distribution (1979–80 odds ratio 1·94, 95% CI 1·10 to 3·41; Mantel-Haenszel χ^2=4·6, p<0·05; 1985–7 odds ratio 3·7, 95% CI 2·3 to 6·0, Mantel-Haenszel χ^2=26·2, p<0·0001).



Two year survival and neurological disability rates/livebirth in 100 g birthweight subgroups for ELBW livebirths in the state of Victoria. This figure compares two eras, 1979–80 (left half of each bar) with 1985–7 (right half of each bar). Sample size is displayed at the top of each column.

Only one infant, born in a level I or level II unit remained there and survived; he was born in 1987, the smaller of discordant twins, birth weight 920 g and gestational age 33 weeks. At 2 years of age he was mildly disabled.

During 1985–7, 49 of 129 (38·0%) of level I or level II births were transferred after birth to a level III centre; 36·7% (18/49) of transferred infants survived to 2 years, a survival rate not significantly different statistically from the 44·8% survival rate of level III centre births (odds ratio 0·72, 95% CI 0·40 to 1·31). The average birth weight of the level I or level II births who were transferred was 817 g; the average birth weight of those remaining in the level I or level II centres was 681 g.

NEURODEVELOPMENTAL OUTCOME AT 2 YEARS OF AGE

In the 1979–80 cohort, 83 of 89 (93·3%) children were assessed at 2 years' corrected age by the research team; alternative professional reports were available on the remaining six children. For the 1985–7 cohort, 206 of 212 (97·2%) children were assessed when aged at least 21 months; alternative professional reports were available on another four; one child was fully assessed at 14 months only and one was untraced, having progressed normally up to 14 months of age. Survivors had similar gestational ages and birth weights in both eras (mean (SD) gestational age (completed weeks): 1979–80, 27·1 (2·4); 1985–7, 27·2 (2·0); mean (SD) birth weight (g): 1979–80, 871 (85); 1985–7, 866 (88)). Significantly more children who survived in the latter era had received intermittent positive pressure ventilation, 77 of 89 (86·5%) in 1979–80 compared with 188 of 196 (95·6%) in 1985–7 (χ^2=6·9, p=0·009); marginally more infants in the latter era had birth weights under the 10th centile (11 of 89 (12·4%) and 44 of 196 (22·4%) respectively; p=0·06, not significant). There were no significant differences in the distribution in the earlier and later eras of the number of multiple births (seven and 28), males (41 and 89), major malformations (none and three) and the highest oxygen requirement over 30% (17 and 30). Sociodemographic data for the survivors were also similar (mean (SD) maternal age in years: 1979–80, 28·4 (4·7); 1985–7, 28·6 (5·2); mother born in a country with English the major language: 1979–80, 71%; 1985–7 80%; mother with less than 10 years schooling: 1979–80, 31%; 1985–7, 21%; and social class—professional, skilled, or semiskilled: 1979–80, 60%; 1985–7, 59%).

The rates of sensorineural impairments in the two cohorts are contrasted in table 1. The rates of cerebral palsy, blindness, deafness, and severe developmental delay were all lower for the 1985–7 era compared with the 1979–80 era, but none of the individual reductions were significant. The mean mental developmental index was significantly higher in 1985–7 (*t*=−3·94, p<0·0001).

In the figure the neurological disability rates/livebirth are illustrated for each era relative to birth weight. Overall, the disability rates/livebirth were similar for both eras, whether just severe disabilities or all disabilities were compared (table 2). On the other hand, the survival rate free of any disability was substantially higher in 1985–7 (26·2%, 147/560), more than doubling that in 1979–80 (12·5% 44/351) (odds

Table 2 Neurological disabilities caused by sensorineural impairments in surviving 2 year old children

	1979–80	*1985–7*
Livebirths	351	560
No (%) of two year survivors	89 (25·4)	212 (37·9)
No with no neurological disabilities:	44	147*
Rate per livebirth (%)	12·5	26·2
Rate per survivor (%)	49·4	69·3
No with neurological disabilities:		
Total	45	64
Rate per livebirth (%)	12·8	11·4
Rate per survivor (%)	50·6	30·2
Mild	25	37
Rate per livebirth (%)	7·1	6·6
Rate per survivor (%)	28·1	17·5
Moderate	4	3
Rate per livebirth (%)	1·1	0·5
Rate per survivor (%)	4·5	1·4
Severe	16	24
Rate per livebirth (%)	4·6	4·3
Rate per survivor (%)	18·0	11·3
No (%) lost to follow up		
Per livebirth	0	1† (0·2)
Per survivor	0	1 (0·5)

*One child with mild hemiplegia was considered to have no disability.

†Free of neurological disabilities and developing normally when last seen at 14 months of age.

Table 1 Sensorineural impairments in surviving 2 year old children

	1979–80	*1985–7*	*Significance*
Livebirths	351	560	
No (%) of two year survivors	89 (25·4)	212 (37·9)	p<0·001
No (%) with cerebral palsy:*	12 (13·5)	15 (7·1)	
Spastic hemiplegia	4	6	
Spastic diplegia	4	4	
Spastic quadriplegia	3	2	
Spastic monoplegia	1	0	
Ataxic	0	1	
Other	0	2	
No (%) with bilateral blindness*	6 (6·7)	9 (4·2)	
No (%) with severe sensorineural deafness*†	3 (3·4)	1 (0·5)	
MDI (2 years):‡			
No of children	79	188	
Mean (SD) MDI	88·1 (19·3)	98·6 (20·1)	*t*=−3·94, p<0·0001
No (%) with MDI <69	12 (13·5)	12 (5·7)	
No (%) with MDI 69–84	23 (25·8)	28 (13·2)	
No (%) with other psychological test 2 SD or more below mean	0	3 (1·4)	
No (%) lost to follow up	0	1 (0·5)	

*% Survivors.

†Requiring amplification.

‡Mental developmental index (MDI) on the Bayley scales of infant development.

ratio 2·29, 95% CI 1·65 to 3·17, $\chi^2=23·7$, p<0·0001).

Overall, with survivors as the denominator and excluding one child in 1985–7 not assessed, disabilities were substantially lower in 1985–7 compared with 1979–80 (Mann-Whitney U test, Z=3·25, p<0·002), but the rates of severe disability were similar in those born in the level III centres (1979–80, 9·9% (7/71); 1985–7, 12·0% (23/193)). In level III survivors, there was a trend overall to fewer disabilities in 1985–7 (in 1979–80: 39 with none, 21 mild, four moderate, and seven severe; in 1985–7: 133 with none, 33 mild, three moderate, and 23 severe; Mann-Whitney U test, Z=1·84, p=0·066). In contrast, in survivors born in level I or level II centres, there was a substantial fall in disability rates overall in 1985–7 (in 1979–80: five with none, four mild, and nine severe; in 1985–7: 14 with none, four mild, and one severe; Mann-Whitney U test, Z=3·14, p<0·002), as well as in severe disabilities alone (1979–80, 50% (9/18); 1985–7, 5·3% (1/19), $\chi^2=7·2$; p<0·01; odds ratio 0·11, 95% CI 0·026 to 0·46).

In the 1979–80 cohort severe disability was significantly more prevalent in surviving children born in level I or level II centres compared with those born in the level III centres (50·0% (9/18) compared with 9·9% (7/71), respectively, odds ratio 14·8, 95% CI 3·9 to 56·3, $\chi^2=13·1$, p<0·001). Within the 1985–7 era, the severe disability rate for those born in level I or level II centres was no longer higher than that for those born in the level III centres (5·3% (1/19) compared with 12·0% (23/192), respectively, odds ratio 0·52, 95% CI 0·12 to 2·27).

Discussion

The improved outcome in the more recent cohort is unlikely to be due to socioeconomic factors, as measured by social and ethnic status and duration of maternal education; neonatal risk factors had not decreased in frequency (male sex, small for gestational age infants, multiple births, high oxygen requirement, use of ventilation, and major malformations). There is a well recognised secular trend for improvement in psychological test scores over time[9]; the increase in mean mental developmental index of over 10 points with only five years separating the two cohorts is too large to make this a likely explanation. Changes in perinatal care practices are the most likely reason for improvement, although the relative importance of individual components remains uncertain.

One of the aims of follow up programmes is to detect potentially avoidable perinatal events that are associated with adverse outcomes, such as death or neurological disability. Having identified an avoidable perinatal event, it is important to take steps to improve the outcome. In our earlier report of the 1979–80 cohort, it was clear that ELBW infants born in level I or level II centres had not only a higher mortality rate, but also a higher rate of severe neurological disabilities in survivors. Educational efforts to improve the early identification of the impending birth of ELBW infants, and their transfer in utero to one of the three level III perinatal centres in the state, had begun in the mid-1970s[10]; these efforts were intensified when the results of the 1979–80 cohort became available. The observation of proportionately fewer ELBW infants being born in level I or level II centres in 1985–7 compared with 1979–80 would suggest that the efforts have been successful.

It will never be possible to have all ELBW infants delivered in level III centres, as some women will present too late to allow sufficient time for their safe transfer before delivery. Educational efforts promoted the prompt transfer whenever possible of ELBW infants born outside level III centres. Whatever criteria have determined whether or not an infant born in a level I or level II nursery was transferred to a level III centre after birth, obviously those selected for transfer have had a better prognosis, as indicated by their higher average birth weight and have survived at a rate approaching that of infants born in the level III centres. Only one surviving ELBW infant, born in 1987, was cared for entirely outside a level III centre.

For the remaining ELBW infants born in level I or level II centres in 1985–7, it is probable that their immediate care has improved. There are more paediatricians who have recently trained in level III centres available to attend deliveries, and on average referrals were made more quickly; a concerted educational programme, available to level I and II personnel was probably another important contributor to improved outcome. Moreover, care during transfer to a level III centre has improved, particularly the ability to monitor transcutaneous oxygen tension continuously.

In the diagnostic field, cranial ultrasound was not widely available in 1979–80 compared with 1985–7, although computed tomography was available in both eras. In 1985–7, however, ventilator support was sometimes withdrawn (after extensive discussion with parents) if a major intracranial haemorrhage was diagnosed.

The improved survival of ELBW infants in the more recent era was not due to a more favourable distribution of birth weight; lack of detailed information on some infants, born and dying outside level III centres in 1979–80 precluded a more detailed analysis. The increased number of ELBW survivors in the latter era is predominantly due to an increased survival rate; there has been a 5% increase in all livebirths over time with only marginal increase in the percentage of ELBW livebirths (0·303% and 0·306%).[1 2]

Of all the innovations in perinatal care in recent times, the ability to assist the ventilation of ELBW infants has probably been the most important in improving their survival. Although ELBW infants comprise only 0·3% of livebirths, they consume more than 50% of ventilator resources. By 1985–7, the resources available for assisted ventilation had been increased substantially by the health care providers in the state. The increase in resources meant that more ELBW infants could be offered assisted ventilation and their survival rate rose in parallel. The improvement in the outcome for ELBW infants in the state has not come cheaply, but aspects of the costs in resources are beyond the scope of this report.

Another aim of follow up programmes is to provide accurate data on long term prognosis. Of necessity, there must be some delay between birth and final outcome. Hence, even the current report relating to 1985–7 births is already up to five years out of date. Nevertheless, it provides the most recent data with which to relate prognosis to birth weight. It is important to note that the outcome for ELBW infants has improved since the 1970s in our state, not only their survival rate, but also regarding long term neurological outcome. In particular, there has been no increase in the absolute number of ELBW children surviving with severe neurological disabilities, yet there have been more than double the number of children surviving free of any disabilities.

Our results differ somewhat from others contrasting the outcome over time of ELBW infants born within the era of modern intensive care. In a geographically defined study like ours, Saigal *et al* reported the outcome of infants of birth weight 501 to 1000 g within the central west region of Ontario in Canada, comparing births during 1977–80 with those during 1981–4.[11] In their study survival rates to hospital discharge were unchanged (46% and 48%, respectively). Children were assessed at 3 years' corrected age, but did not have formal developmental or intellectual testing. In survivors, neurosensory impairment rates (24% and 17%, respectively) and severe functional disability rates (4·5% and 4·1%, respectively) were similar, although there was a significant reduction in all functional disabilities (50% to 27%, respectively). In a further contrast with our study, Saigal *et al* reported the survivors born in a level I or level II centre continued to have more neurological impairments in their latter era (level I or II survivors 37%; level III survivors 14%).[11]

In an earlier study, Saigal *et al* reported the outcome of survivors of birth weight 501 to 1000 g born to residents of the Hamilton-Wentworth County alone, not the whole central west region of Ontario[12]; they compared those born in 1973–6 with those born in 1977–80. Survival rose from 23·7% to 48·8% and the rate of functional disability in survivors remained unchanged (55·6% and 52·6% respectively). Results were not reported separately for infants born to residents of Hamilton-Wentworth County alone in 1981–4,[11] but it is probable that, in comparison with those born in 1973–6, both mortality rates and functional disability rates would have fallen over time as in our study.

In a single hospital study reported by Hack and Fanaroff the outcome for infants with birth weights <750 g born between July 1982 and June 1985 was compared with those born between July 1985 and June 1988.[13] Survival rates were almost identical (20% and 18%, respectively); the apparent change in moderate/severe neurological impairment rates (22% to 50%) between the two eras was not significant. Hoffman and Bennett reported their tertiary centre's experience for infants with birth weights <800 g admitted to their intensive care nursery; over time, the survival rate rose from 20% to 36%, but the survivors had more severe neurological impairments.[14] Our results are more like those of Kilbride *et al* who, in a single hospital study, reported that both mortality and disability rates were lower in infants of birth weight 401 to 800 g born in 1983–5, compared with those born in 1980–2.[15] In our cohort, both survival and neurological outcome improved in the latter era for children with birth weights <800 g (figure).

In our geographically based study, as perinatal care has improved over time and as the resources available to assist ventilation have increased, the outcome for ELBW infants has improved, with substantially lower two year mortality and neurological morbidity rates. Further geographically based studies will be needed to assess the impact of any future changes in perinatal care.

Supported by the Health Department, Victoria, the Royal Women's Hospital-3AW Clinical Research Foundation, and the Monash Medical Fund.

1 Kitchen W, Ford G, Orgill A, *et al*. Outcome of infants with birth weight 500 to 999 gm: a regional study of 1979 and 1980 births. *J Pediatr* 1984;**104**:921–7.

2 Consultative Council on Obstetric and Paediatric Mortality and Morbidity. *Annual reports for the years 1985 to 1987*. Melbourne: Government Printer, 1986–1989.

3 Roy RND, Kitchen WH. NETS: a new system for neonatal transport. *Med J Aust* 1977;**2**:855–8.

4 Bayley N. *Bayley scales of infant development*. New York: Psychological Corporation. 1969.

5 Kitchen WH, Yu VYH, Orgill AA, *et al*. Collaborative study of very-low-birth weight infants. *Am J Dis Child* 1983;**137**: 555–9.

6 Yusuf S, Peto R, Lewis T, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of randomised trials. *Prog Cardiovasc Dis* 1985;**27**: 336–71.

7 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719–48.

8 Moses LE, Emerson JD, Hosseini H. Analyzing data from ordered categories. *N Engl J Med* 1984;**311**:442–6.

9 Flynn JR. Massive IQ gains in 14 nations. What IQ tests really measure. *Psychol Bull* 1987;**101**:171–91.

10 The Consultative Council on Maternal and Perinatal Mortality. *16th Annual report for the year 1977*. Victoria: Department of Health, 1977.

11 Saigal S, Rosenbaum P, Hattersley B, Milner R. Decreased disability rate among 3-year-old survivors weighing 501 to 1000 grams at birth and born to residents of a geographically defined region from 1981 to 1984 compared with 1977 to 1980. *J Pediatr* 1989;**114**:836–46.

12 Saigal S, Rosenbaum P, Stoskopf B, Sinclair JC. Outcome in infants 501 to 1000 gm birth weight delivered to residents of the McMaster Health Region. *J Pediatr* 1984;**105**: 969–76.

13 Hack M, Fanaroff AA. Outcomes of extremely-low-birth weight infants between 1982 and 1988. *N Engl J Med* 1989; **321**:1642–7.

14 Hoffman EL, Bennett FC. Birthweight less than 800 grams: changing outcomes and influences of gender and gestation number. *Pediatrics* 1990;**86**:27–34.

15 Kilbride HW, Daily DK, Claflin K, Hll RT, Maulik D, Grundy HO. Improved survival and neurodevelopmental outcome for infants less than 801 grams birthweight. *Am J Perinatol* 1990;**7**:160–5.

Archives of Disease in Childhood 1991; **66:** 770–775

Multicentre randomised controlled trial of high against low frequency positive pressure ventilation

Oxford Region Controlled Trial of Artificial Ventilation (OCTAVE) Study Group

Abstract

A total of 346 infants aged <72 hours were randomly allocated to be treated either by high frequency positive pressure ventilation (HFPPV; rate fixed at 60/minute throughout treatment and initial inspiratory:expiratory (I:E) ratio 1:2, increased to 1:1 if necessary) or by low frequency positive pressure ventilation (LFPPV; rate ≤40/minute and initial I:E ratio usually 1:1, both decreasing during weaning). The main hypotheses were that HFPPV reduces pneumothorax, chronic lung disease and death before discharge in all infants, as well as those with hyaline membrane disease, and that it reduces the incidence of later neurodevelopmental complications in infants of <33 weeks' gestation. Among all the infants the rate of pneumothorax was 19% in the HFPPV group and 26% in the LFPPV group ($p=0\cdot13$; odds ratio 0·7, 95% confidence intervals (CI) 0·4 to 1·1); there was no difference in mortality or the incidence of chronic lung disease. In infants of <33 weeks' gestation there were no differences in adverse neurodevelopmental outcomes. Among the subgroup of 237 infants with hyaline membrane disease, median fractional inspired oxygen at the time of entry to the trial was 0·6 in the HFPPV group and 0·7 in the LFPPV group, indicating that many had moderately severe disease. In patients with hyaline membrane disease HFPPV was associated with a lower rate of pneumothorax (18% in the HFPPV group compared with 33% in the LFPPV group, $p=0\cdot013$, odds ratio 0·5, 95% CI 0·3 to 0·8), with no differences in mortality, or in duration of intubation or supplementary oxygen in survivors. As used in this study, HFPPV was the preferred ventilator regimen for infants with hyaline membrane disease.

John Radcliffe Maternity Hospital and Oxford Region Hospitals
OCTAVE Study Group

Correspondence to:
Dr WO Tarnow-Mordi,
Centre for Research in Human Development,
Department of Child Health,
Ninewells Hospital
and Medical School,
Dundee DD1 9SY.

Accepted 4 February 1991

Artificial ventilation for newborn infants has been associated with substantially increased survival.[1–4] The risks of pneumothorax[5 6] and chronic lung disease[7] seem to have increased, however, and the question of which methods of artificial ventilation are safest remains controversial.[8 9]

Until recently most ventilator regimens used in the United Kingdom specified rates of <40/minute.[2] Several studies, some uncontrolled,[10–12] one in which treatment regimens were allocated alternately,[13] and one that was randomly controlled,[14] have suggested that higher ventilator rates (≥60 cycles/minute) may reduce the incidence of pneumothorax. These studies did not, however, always describe outcomes in hyaline membrane disease (the main cause of neonatal respiratory illness) and were too small to assess the effects of the ventilator regimen on mortality or the incidence of chronic lung disease. We therefore undertook a randomised controlled trial in which the following hypotheses were tested: compared with low frequency positive pressure ventilation (LFPPV) at 20–40 cycles/minute, high frequency positive pressure ventilation (HFPPV) at 60 cycles/minute reduces the incidence of pneumothorax, the number of deaths before discharge from hospital, and the incidence and severity of chronic lung disease in survivors, in infants of all diagnostic categories as well as in infants with hyaline membrane disease alone; and reduces long term neurodevelopmental impairment and disability in surviving infants of less than 33 weeks' gestation.

Patients and methods

The study was conducted between October 1983 and September 1986 in six hospitals in the Oxford health region. The study design was approved by the ethics committees of all participating hospitals. Formal parental consent for entry to the trial and random assignment to HFPPV or LFPPV was not sought because ventilator frequencies of 20–60 cycles/minute or more were already in use in the hospitals. (Copies of a submission to the Central Oxford Research Ethics Committee are available on request.) Parents were seen as soon as possible during the 48 hours after birth, given an information leaflet, and encouraged to ask questions at any time. No parents asked that the allocated regimen be changed, but had any done so we would have respected their wishes, providing that there were no clinical contraindications.

ELIGIBILITY AND TRIAL ENTRY

Infants were eligible if they were <72 hours old, if they were receiving positive pressure ventilation by endotracheal tube at ≥20 cycles/minute, if there was no sign of meconium aspiration, and if a Sechrist IV 100B ventilator was available. With the possible exception of meconium

---

Members of the OCTAVE Study Group included: John Radcliffe Maternity Hospital: AR Wilkinson, P Cadman, WO Tarnow-Mordi (trial coordinator). Wexham Park and Heatherwood Hospitals: J Cowen, J Pearce. Milton Keynes Hospital: V Joss. Wycombe General Hospital: C Cheetham, H Fleet. Kettering General Hospital: A Mukhtar. National Perinatal Epidemiology Unit, Oxford: D Elbourne, A Grant, I Chalmers. Oxford Region Child Development Project: A Johnson, R King. Department of Community Medicine, Ninewells Hospital and Medical School: S Ogston.

aspiration, precise respiratory diagnoses are not always apparent when mechanical ventilation is begun during the first few hours of life. Apart from meconium aspiration, therefore, the trial was open to all babies who met the entry criteria regardless of the indications for mechanical ventilation.

TRIAL ENTRY AND RANDOM ALLOCATION OF VENTILATOR REGIMEN

The trial was coordinated from the intensive care nursery at the John Radcliffe Maternity Hospital. Random assignment of ventilator management to LFPPV or HFPPV was done after admission by opening the next sealed, opaque, serially numbered envelope held in a box at the nursing station. Staff at the other five participating hospitals telephoned the neonatal unit at the John Radcliffe Hospital for each baby's treatment allocation. The randomisation was stratified by clinical centre only.

DIAGNOSTIC CRITERIA FOR HYALINE MEMBRANE DISEASE

Hyaline membrane disease was diagnosed if an infant had chest wall retractions and a radiograph showing reticulogranular densities or a 'ground glass' appearance, or diffuse opacification with air bronchograms, and required supplementary oxygen increasingly during the first day and supplementary oxygen was required for at least 72 hours, reaching at least 30%.

TRIAL MANAGEMENT

Ventilator rates, inspiratory:expiratory (I:E) ratios, gas flow rates, and the recommended plan of management are shown in the Appendix. No infant received surfactant. In each regimen, the ventilator pressures initially chosen were those that produced adequate expansion of the chest wall. Subsequent ventilator settings were adjusted to maintain blood gas tensions within the range: arterial oxygen tension (Pao_2) 6·7–10·7 kPa (50–80 mm Hg), arterial carbon dioxide tension ($Paco_2$) 4–6 kPa (30–45 mm Hg), and pH 7·25–7·45. Pancuronium was reserved for infants who were considered to be struggling excessively against the ventilator.[5] Mean airway pressure was measured electronically at the proximal airway, with a Sechrist APM or an Insight 2000 monitor, or by needle gauge manometers (PP Electronics) connected to the proximal airway by a high resistance restrictor device.

CRITERIA FOR RELAXATION OF ALLOCATED VENTILATOR MANAGEMENT

The allocated regimen could be relaxed if any of the following criteria were met: poor gas exchange defined as Pao_2 <6·7 kPa (<50 mm Hg) despite fractional inspired oxygen (Fio_2) >0·95 and mean airway pressure of 17 cm H_2O, or $Paco_2$ >7·3 kPa (>55 mm Hg) despite using the maximum recommended ventilator rate at a mean airway pressure of 17 cm H_2O; recurrent pneumothorax, defined as the insertion of two or more chest drains to treat pneumothorax; or chronic ventilator dependence, defined as still receiving mechanical ventilation at 28 days of age.

Before relaxing planned management because of poor gas exchange, measures to reduce extrapulmonary right to left shunt were considered. These included infusion of plasma, blood, or dopamine to keep mean systemic blood pressure >25 mm Hg in infants of <1000 g birth weight and >30 mm Hg in larger infants. If the systemic blood pressure was above these values, infusion of tolazoline was also considered. All other aspects of clinical management were left to the discretion of the neonatologist responsible for care.

LONG TERM NEURODEVELOPMENTAL ASSESSMENT IN SURVIVORS BORN AT LESS THAN 33 WEEKS' GESTATION

Although we had originally planned to compare the rates of periventricular haemorrhage in infants <33 weeks' gestation it was not possible to obtain cerebral ultrasound scans from all centres. This outcome measure was therefore replaced by a comparison of longer term neurodevelopmental assessments, which were obtained from the impairment register kept by the Oxford Region Child Development Project, or (for children not resident in the region, from the responsible paediatrician) using a classification which has been described elsewhere.[15]

ANTICIPATED SAMPLE SIZE

We estimated that a trial with 174 infants in each group would have a good chance (90% power) of identifying a reduction in pneumothorax in all infants from an expected rate of 30% to 15% (2p <0·05). Assuming that 70% of all mechanically ventilated infants had hyaline membrane disease and that hyaline membrane disease carries a higher risk of pneumothorax, a trial of this size would also have a 90% chance of identifying a reduction in pneumothorax from 40% to 20% at a similar level of significance.[16]

STATISTICAL ANALYSIS

All analyses were based on the regimen randomly assigned, regardless of subsequent ventilator management. The significance of differences in proportions were analysed by the χ^2 test with Yates's correction or Fisher's exact test. Normally distributed continuous variables were compared by a parametric test (unpaired *t* test), and skewed continuous variables by the Mann-Whitney U test. The effects of any imbalances in important prognostic variables between trial groups[17] were investigated by multiple logistic regression.[18]

Results

TRIAL GROUPS AT ENTRY

A total of 346 infants were recruited to the trial. Descriptive variables for all infants and for infants with hyaline membrane disease are shown in table 1. The groups were similar except that, among infants with hyaline membrane disease, those who were assigned to the HFPPV group tended to be more mature and heavier than those assigned to receive LFPPV. There was no difference in the overall proportions of infants in whom allocated management was relaxed (table 2).

MANAGEMENT RECEIVED

The allocated ventilator regimen was relaxed in between 24–29% of infants in each group, usually because of poor gas exchange (table 2). Although the regimen was relaxed because of recurrent pneumothorax more often in infants assigned to receive LFPPV, this difference was not significant. Overall, relaxation of the allocated regimen occurred more often because of chronic ventilator dependence in those assigned to HFPPV (p=0·03 by Fisher's exact test, two tailed).

SPECIFIED ANALYSES OF OUTCOME

Overall there were no clear differences in any major outcome between the two groups. The odds of both death before discharge and pneumothorax were lower in the HFPPV group, but neither difference was significant (table 3). Among infants with hyaline membrane disease, however, pneumothorax after randomisation was 18% in the HFPPV group and 33% in the LFPPV group (p=0·013, odds ratio 0·5, 95% Cl 0·3 to 0·8) (table 3). Infants with hyaline membrane disease who were allocated to receive HFPPV showed a trend to lower hospital mortality (HFPPV 17% compared with LFPPV 28%; p=0·06, odds ratio 0·5, 95% Cl 0·3 to 1·0), but there were no differences in the proportions of survivors who received mechanical ventilation or added oxygen at 29 days, in their median oxygen requirement at 29 days, their median age at final extubation, or the median age when supplementary oxygen was discontinued (table 3).

The main diagnoses in infants who did not have hyaline membrane disease included transient tachypnoea, pneumonia, recurrent apnoea, persistent fetal circulation, and birth asphyxia. There were no significant differences in any outcome in any of these categories. In surviving infants of <33 weeks' gestation (in 98% of whom follow up assessments were

Table 1 Characteristics of infants at trial entry. Data are expressed as number (%) unless otherwise stated

	All infants		*Infants with hyaline membrane disease*	
	HFPPV (n=174)	*LFPPV (n=172)*	*HFPPV (n=123)*	*LFPPV (n=114)*
Mean (SD) birth weight (g)	1596 (752)	1541 (829)	1493 (583)	1323 (606)
Mean (SD) gestation (weeks)	31·0 (3·7)	30·5 (4·2)	30·4 (3·0)	29·3 (3·0)
Median (range) age (hours)	3·0 (0–71)	3·0 (0–71)	3·0 (0–50)	3·0 (0–71)
Median (range) FIO$_2$	0·6 (0·21–1·0)	0·6 (0·21–1·0)	0·6 (0·30–1·0)	0·7 (0·32–1·0)
Boys	100 (57)	98 (57)	73 (59)	70 (61)
Inborn	154 (89)	150 (87)	107 (87)	96 (84)
Birth weight <10th centile	24 (14)	22 (13)	16 (13)	13 (11)
Apgar score <7 at 5 minutes	50 (29)	41 (24)	31 (25)	26 (23)
Intubated at birth	111 (64)	128 (74)	77 (63)	83 (73)
Pneumothorax before entry	4 (2)	5 (3)	1 (1)	2 (2)

Table 2 Reasons for relaxation of allocated ventilator regimen. Data are expressed as number (%)

	All infants		*Infants with hyaline membrane disease*	
	HFPPV (n=174)	*LFPPV (n=172)*	*HFPPV (n=123)*	*LFPPV (n=114)*
Allocated ventilator regimen relaxed:	47 (27)	43 (25)*	30 (24)	33 (29)**
Poor gas exchange	19 (40)	22 (51)	12 (40)	17 (52)
Air leak	2 (4)	7 (16)	2 (7)	6 (18)
Chronic ventilation	6 (13)	0	2 (7)	0
Other reasons	20 (43)	14 (33)	14 (47)	10 (30)

*p=0·76, odds ratio 1·1 (95% CI 0·7 to 1·8); **p=0·51, odds ratio 0·8 (95% CI 0·4 to 1·4).

Table 3 Short term measures of outcome. Data are expressed as number (%) except where otherwise stated

	All infants				*Infants with hyaline membrane disease*			
	HFPPV (n=174)	*LFPPV (n=172)*	*p Value*	*Odds ratio (95% CI)*	*HFPPV (n=123)*	*LFPPV (n=114)*	*p Value*	*Odds ratio (95% CI)*
Whole group:								
Pneumothorax after entry	32/170 (19)	44/167 (26)	0·13	0·7 (0·4 to 1·1)	22/122 (18)	37/112 (33)	0·013	0·5 (0·3 to 0·8)
Deaths before discharge	41/174 (24)	50/172 (29)	0·16	0·8 (0·5 to 1·2)	21/123 (17)	32/114 (28)	0·06	0·5 (0·3 to 1·0)
Survivors:								
IPPV after 28th day	19/133 (14)	17/122 (14)	0·90	1·0 (0·5 to 2·1)	17/102 (17)	12/82 (15)	0·88	1·2 (0·5 to 2·6)
Supplementary oxygen after 28th day	42/133 (32)	38/122 (31)	0·94	1·0 (0·6 to 1·7)	37/102 (36)	27/82 (33)	0·64	1·2 (0·6 to 2·1)
Median (range) FIO$_2$ at 29th day	0·21 (0·21–0·6)	0·21 (0·21–0·55)	0·83	—	0·21 (0·21–0·6)	0·21 (0·21–0·55)	0·69	—
Median (range) age (days) when finally extubated	4·0 (0–164)	5·0 (0–183)	0·49	—	4·4 (0–164)	6·0 (0–144)	0·21	—
Median (range) age (days) when finally breathed added oxygen	9·0 (1–796)	9·0 (0–242)	0·5	—	10·4 (1–796)	12·0 (0–242)	0·76	—

Table 4 Long term outcome for infants of less than 33 weeks' gestation. Data are expressed as number (%) except where otherwise stated

	HFPPV	*LFPPV*	*Odds ratio (95% CI)*
Total No recruited	125	126	—
Mean (SD) gestation (weeks)	28·6 (4·5)	28·1 (5·3)	—
Median (range) age (months) when last seen	18 (3–48)	18 (18–64)	—
Deaths during first year	36 (29)	29 (23)	1·4 (0·8 to 2·4)
Deaths after 1 year of age	0	1 (1)	0·1 (0 to 6·8)
Lost to follow up	2 (2)	6 (6)	0·4 (0·1 to 1·5)
No of infants surviving longer than 1 year*	87	90	—
Normal outcome	69 (79)	69 (77)	1·2 (0·6 to 2·4)
Cerebral palsy	4 (5)	12 (13)	0·4 (0·1 to 1·0)
Other central nervous system disease	2 (2)	5 (6)	0·4 (0·1 to 1·9)
Severe hearing impairment	4 (5)	8 (9)	0·4 (0·1 to 1·3)
Severe visual impairment	6 (7)	13 (14)	0·5 (0·2 to 1·2)
Global developmental delay	4 (5)	6 (7)	0·7 (0·2 to 2·4)

*Percentages total more than 100 because some infants had more than one condition.

Table 5 Use of pancuronium at the John Radcliffe Hospital

	All infants		*Infants with hyaline membrane disease*	
	HFPPV (n=127)	*LFPPV (n=128)*	*HFPPV (n=90)*	*LFPPV (n=79)*
No (%) that received pancuronium	40 (31)	26 (20)*	30 (33)	20 (25)**

*p=0·058; odds ratio 1·8 (95% CI 1·0 to 3·1); **p=0·33; odds ratio 1·5 (95% CI 0·8 to 2·8)

'blind'), those allocated to receive HFPPV showed no increase in neurodevelopmental complications or abnormal outcomes (table 4).

ANALYSES OF OUTCOME NOT SPECIFIED IN ADVANCE

Survivors of <33 weeks' gestation who had been allocated HFPPV had a marginally lower rate of severe neuromotor impairment ('cerebral palsy'), a finding that could have been due to chance.

The analyses restricted to infants with hyaline membrane disease were adjusted by multiple logistic regression for possible confounding effects of gestational age, birth weight, and sex.[17,18] The difference in the rate of pneumothorax between regimens remained significant, but the difference in mortality did not.

Data on the use of pancuronium were obtained only for infants at the John Radcliffe Hospital. These showed a trend toward increased use of pancuronium in the HFPPV group (p=0·058, odds ratio 1·8, 95% CI 1·0 to 3·1) (table 5). By multiple regression analysis, both HFPPV and pancuronium were found to be independently associated with a reduction in the incidence of pneumothorax (p<0·001). The apparent protective effect was considerably greater for pancuronium than for HFPPV, both in all infants and in those with hyaline membrane disease.

Discussion

The most valid comparisons of ventilator techniques are likely to come from studies that meet two conditions. Firstly, ventilator techniques should be randomly assigned within each hospital. This tends to balance the innumerable variables that affect prognosis (whether known or not) evenly between the treated and control groups.[19,20] Secondly, the trial should recruit large enough numbers of infants to allow a distinction to be made between real and chance differences in outcome. Although this trial is to our knowledge the largest randomised study of conventional neonatal ventilation yet reported, it was likely (with 90% power) to show a significant result only if the true effects were large (a 50% reduction in pneumothorax or a correspondingly greater reduction in chronic lung disease).

Overall we found that HFPPV was associated with a 34% reduction in the odds of pneumothorax, which did not reach our preset level of significance. Among infants with hyaline membrane disease, however, in whom we had postulated a greater risk of pneumothorax, HFPPV was associated with a 50% reduction in the odds of pneumothorax (p=0·013; odds ratio 0·5, 95% CI 0·3 to 0·8). This is important, and when data from the only comparable trial are taken into account (table 6),[13] it seems unlikely that the observed difference in the incidence of pneumothorax in both trials is due to chance. There were no clear differences in mortality or in the development of chronic lung disease between the groups, and the proportions of survivors of less than 33 weeks' gestation with normal outcome were similar (table 4).

Our results seem to conflict with those of Reynolds and Taghizadeh,[2] who compared ventilator frequencies of 30–40/minute and I:E ratios of 1:1 with frequencies of 60–80/minute and I:E ratios of 1:2, similar to the technique of HFPPV that we used. They found more deaths and no reduction in the incidence of

Table 6 Meta-analyses of controlled trials of HFPPV against LFPPV

	Odds ratio	*95% CI*
Effect of HFPPV on relative odds of pneumothorax in all infants:		
Heicher *et al*, 1981[13]	0·3	0·1 to 0·8
OCTAVE, 1990	0·7	0·4 to 1·1
Typical odds ratio	0·6	0·4 to 0·9
Effect of HFPPV on relative odds of death among all infants:		
Heicher *et al*, 1981[13]	0·8	0·3 to 1·8
OCTAVE, 1990	0·8	0·5 to 1·2
Typical odds ratio	0·8	0·5 to 1·2

pneumothorax with faster frequencies. The two studies are not necessarily at variance, however, because the equipment, the methods, and the infants were not comparable. In the earlier study an intermittent flow ventilator (Bennett PR2) was used,[2] in which mean airway pressure—and hence oxygenation[21–23]—decreased at frequencies above 40/minute.[23] Most (but not all) modern continuous flow ventilators maintain mean airway pressure at faster frequencies,[24] particularly if the gas flow rate is increased (Appendix).[25] In the earlier study the infants treated with fast frequencies were born between 1967 and 1969, and the second group between 1970 and 1972. Some of the reduction in mortality in the second group may thus have resulted from factors other than ventilator management. All the infants in the earlier study had severe hyaline membrane disease,[2] because mechanical ventilation was begun when the infants were apnoeic; or gasping, peripherally vasoconstricted and bradycardic; or had $\mathrm{PaO_2}$ $\leqslant$4·7 kPa (35 mm Hg) and $\mathrm{FIO_2}$ $\geqslant$0·95.[2] This is a crucial difference because many infants in the present trial had moderate hyaline membrane disease, with $\mathrm{PaO_2}$ >6·7 kPa (50 mm Hg) and a median $\mathrm{FIO_2}$ of 0·6 or 0·7 at entry (table 1). In moderate hyaline membrane disease we found that adequate oxygenation was possible using HFPPV with an I:E ratio of 1:2 at relatively low peak and end expiratory pressures. In severe hyaline membrane disease, however, an I:E ratio of 1:2 in HFPPV was not appropriate because peak pressures of >30 cm H_2O were frequently required to maintain oxygenation.[2 21] In severe hyaline membrane disease, therefore, we routinely increased the I:E ratio from 1:2 to 1:1 and the inspiratory time from 0·33 to 0·5 seconds (Appendix) to improve alveolar inflation and gas exchange.[2 9 21 26]

How might HFPPV protect against pneumothorax? If pneumothorax occurs when lung units overinflate, the risk is likely to be greater when the ventilator delivers larger tidal volumes, particularly if these are superimposed on the infant's own inspiration. Greenough *et al* observed that when this occurred in infants receiving LFPPV—that is, when a one second ventilator inflation took place within 0·2 seconds of the end of spontaneous inspiration, it provoked asynchronous breathing with 'active expiration' against the ventilator (the infant forcibly exhaled during the ventilator peak pressure phase).[27] This may be an example of the Hering-Breuer reflex in response to stimulation of vagally innervated stretch receptors resulting from overinflation[28] and gas trapping. Field *et al* reported that active expiration was reduced by increasing the ventilator rate or reducing the I:E ratio.[29] Both these manoeuvres reduce tidal volume and together result in a ventilator technique similar to the method of HFPPV used here. HFPPV may therefore protect against pneumothorax by preventing overinflation of lung units, coincidentally reducing active expiration.

Among infants receiving LFPPV Greenough *et al* found that pancuronium considerably reduced the risk of pneumothorax in those with active expiration.[30] Using multiple regression analysis we found that pancuronium given when infants struggled excessively against the ventilator had a substantial apparently protective effect against pneumothorax, which was independent of that of HFPPV.

In this study, LFPPV usually entailed an initial I:E ratio of 1:1 at 20–40 cycles/minute with relatively long inspiratory times of 0·75–1·0 seconds (Appendix). Except in very stiff lungs, increased inspiratory times may predispose to pneumothorax because of overinflation and gas trapping,[31] and to obstruction of the pulmonary circulation. This type of LFPPV is probably particularly inappropriate for infants with less severe hyaline membrane disease, which will become more common with the use of surfactant or antenatal steroids.

This study shows that there is a growing need for multicentre collaboration if methods of reducing pneumothorax, mortality from chronic lung disease, and adverse neurodevelopmental outcome are to be evaluated reliably. If these outcomes become progressively less common, larger numbers will be needed,[16] so it would be valuable to establish a national network of paediatricians willing to cooperate in future trials. National (and international) agreement on a standard format for data collection will be helpful, so that uniform measures of initial severity of disease and outcome can be made.[32] If no adverse interaction between treatments is expected there is no scientific reason why randomised trials that are designed to answer different questions should not take place simultaneously in the same neonatal units. Indeed, this should be encouraged so that our uncertainties about the most effective treatments can be resolved more rapidly.

WOT-M was an Action Research Training Fellow. We thank the parents and nursing and medical staff in all the units that took part, for their patience, humour, and commitment. The work was supported by Action Research for the Crippled Child, the Department of Health, Children Nationwide, the Scottish Chest Heart and Stroke Association, and the Scottish Home and Health Department. We thank Mutitta Fletcher, Paul Griffiths, Hazel Ashurst, and Beth Reid for help with data analysis; and Gunnar Sedin, Karin Hammarlund, Andy Ramsden, David Baum, Tony Williams, Lesley Mutch, Sir Peter Tizard, and Sir Eric Stroud for advice and encouragement.

1 Reid DHS, Tunstall ME, Mitchell RG. A controlled trial of artificial respiration in the respiratory distress syndrome of the newborn. *Lancet* 1967;i:532–3.
2 Reynolds EOR, Taghizadeh A. Improved prognosis of infants mechanically ventilated for hyaline membrane disease. *Arch Dis Child* 1974;**49**:505–15.
3 Stewart AL, Reynolds EOR, Lipscomb AP. Outcome for infants of very low birthweight: survey of world literature. *Lancet* 1981;i:1038–40.
4 Horwood SP, Boyle MH, Torrance GW, Sinclair JC. Mortality and morbidity of infants of 499–1500 grams birthweight liveborn to residents of a defined geographic region before and after neonatal intensive care. *Pediatrics* 1982;**69**:613–20.
5 Tarnow-Mordi WO, Narang A, Wilkinson AR. Lack of association between barotrauma and air leak in hyaline membrane disease. *Arch Dis Child* 1985;**60**:555–9.
6 Greenough A, Roberton NRC. Morbidity and survival in infants ventilated for the respiratory distress syndrome. *BMJ* 1985;**290**:597–600.
7 Tooley WH. Epidemiology of bronchopulmonary dysplasia. *J Pediatr* 1979;**95**:851–5.
8 Avery ME, Tooley WH, Keller JB, *et al*. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;**79**:26–30.
9 Ramsden CA, Reynolds EOR, Morley C, South M, Milner AD. Controversy: ventilator settings for newborn infants. *Arch Dis Child* 1987;**62**:529–38.
10 Sedin G. Positive pressure ventilation at moderately high frequency in newborn infants with respiratory distress syndrome (IRDS). *Acta Anaesthesiol Scand* 1986;**30**:515–20.
11 Bland RD, Kim MH, Light MJ, Woodson JL. High frequency mechanical ventilation in severe hyaline membrane

disease. An alternative treatment? *Crit Care Med* 1980;**8**: 275–80.

12 Eyal FG, Arad ID, Godder K, *et al.* High frequency positive pressure ventilation in neonates. *Crit Care Med* 1984;**12**: 793–7.

13 Heicher DA, Kastings DS, Harrod JR. Prospective clinical comparison of two methods for mechanical ventilation of neonates: rapid rate and short inspiratory times versus slow rate and long inspiratory time. *J Pediatr* 1981;**98**:956–61.

14 Pohlandt F, Bernsau U, Feilen KD, *et al.* Reduction of barotrauma in ventilated neonates by increase in ventilation frequency—first results of a prospective collaborative and randomized trial of two different ventilator techniques. *Pediatr Res* 1985;**19**:1077.

15 Johnson A, King R. A regional register of early childhood impairment: a discussion paper. *Community Med* 1989; **11**:352–63.

16 Fleiss JL. *Statistical methods for rates and proportions.* 2nd Ed. New York: Wiley, 1981.

17 Altman DG. Comparability of randomised groups. *Statistician* 1985;**34**:125–36.

18 Baker R, Nelder JA. *The GLIM System, version 3.* Oxford: Numerical algorithms group, 1978.

19 Fisher RA. *The design of experiments.* 8th Ed. Edinburgh: Oliver and Boyd, 1966.

20 Byar DP, Simon RM, Friedewald WT, *et al.* Randomized clinical trials. Perspectives on some recent ideas. *N Engl J Med* 1976;**295**:74–80.

21 Herman S, Reynolds EOR. Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. *Arch Dis Child* 1973;**48**:612–17.

22 Boros SJ. Variations in inspiratory:expiratory ratio and airway pressure wave form during mechanical ventilation: the significance of mean airway pressure. *J Pediatr* 1979; **94**:114–7.

23 Boros SJ, Campbell K. A comparison of the effects of high frequency-low tidal volume and low frequency-high tidal volume mechanical ventilation. *J Pediatr* 1980;**97**:108–12.

24 Boros SJ. Using conventional infant ventilators at unconventional rates. *Pediatrics* 1984;**74**:487–92.

25 Greenough A, Pool J, Greenall F, Morley C, Gamsu H. Comparison of different rates of artificial ventilation in preterm neonates with respiratory distress syndrome. *Acta Paediatr Scand* 1987;**76**:706–12.

26 Stewart AL, Finer NN, Peters KL. Effects of alterations of inspiratory and expiratory pressures and inspiratory: expiratory ratios on mean airway pressure, blood gases and intracranial pressure. *Pediatrics* 1981;**67**:474–81.

27 Greenough A, Morley CJ, Johnson P. An active expiratory reflex in preterm ventilated infants. In: Jones CT, Nathanielsz PW, eds. *The physiological development of the fetus and newborn.* New York: Academic Press, 1985: 259–63.

28 Hering E. Self-steering of respiration through the nervus vagus. *Sitzungsberichte der Kaiserlichen Akadamie der Wissenschaften zu Wien* 1869;**60**:838. Translated by Ullmann E. In: Porter R, ed. *Breathing: Hering-Breuer Centenary Symposium.* London: Churchill, 1970:359.

29 Field DJ, Milner AD, Hopkin IE. Manipulation of ventilator settings to prevent active expiration against positive pressure ventilation. *Arch Dis Child* 1985;**60**:1036–40.

30 Greenough A, Wood S, Morley CJ, Davis JA. Pancuronium prevents pneumothoraces in ventilated premature infants who actively expire against positive pressure inflation. *Lancet* 1984;**i**:1–4.

31 Primhak RA. Factors associated with pulmonary air leak in premature infants receiving mechanical ventilation. *J Pediatr* 1983;**102**:764–8.

32 Tarnow-Mordi WO, Ogston S, Wilkinson AR, *et al.* Predicting death from initial disease severity in very low birth weight infants: a method for comparing the performance of neonatal units. *BMJ* 1990;**300**:1611–4.

Appendix

	*High frequency positive pressure ventilation (HFPPV)**		*Low frequency positive pressure ventilation (LFPPV)*
Typical starting settings:			
PIP	17–25 cm H_2O		15–25 cm H_2O
PEEP	4–6 cm H_2O		3–5 cm H_2O
Gas flow rate	6–8 l/min		6–8 l/min
Ventilator rate	60/min	Fixed throughout (but see (a) below and footnote**)	30 (20–40)/min
Inspiratory:expiratory ratio	1:2		1:1
Inspiratory time	0·33 sec		(but at rates <30/min, inspiratory time is usually set at 1·0 sec)
Expiratory time	0·67 sec		
If Pao_2 high:	Decrease FIO_2 or PIP or PEEP		Decrease FIO_2 or PIP or PEEP or I:E ratio
If Pao_2 low	Increase FIO_2 or PIP or PEEP		Increase FIO_2 or PIP or PEEP or I:E ratio
If Paco_2 high	Increase PIP or decrease PEEP (often unwise in early HMD)		Increase rate (to maximum 40/min) or increase PIP or decrease PEEP (often unwise in early HMD)
If Paco_2 low	Decrease PIP or rate** or increase PEEP		Decrease rate or PIP or increase PEEP

When MAP reaches 12 cm H_2O and FIO_2 >0·6 (severe disease)

(i) Increase gas flow rate to 8–10 l/min for a better square pressure waveform. If using Fisher Paykel humidifier with standard adult chamber, change to low compressible volume chamber. Readjust PIP and PEEP to the same values if necessary

(ii) If using Bennett Cascade or similar water bath humidifier, keep it filled to maximum and increase gas flow (10–12 l/min with Bennett) for better square pressure waveform

	If Pao_2<6·7 kPa and FIO_2>0·95 when MAP=12 cm H_2O or if Paco_2 >7·3 kPa when MAP=12 cm H_2O	If Pao_2<6·7 kPa and FIO_2=0·95 when MAP=12 cm H_2O or if Paco_2>7·3 kPa when rate=40/min
	(a) **Increase I:E ratio from 1:2 to 1:1 (so inspiratory time=expiratory time=0·5 sec). Important:** you may have to cut PIP by 1–5 cm, to avoid excessive chest wall expansion. (b) Check blood gases in 15 minutes (c) Consider treating hypotension or extrapulmonary right to left shunting (for example, infusion of plasma, blood, dopamine, tolazoline, or 1 mmol/kg alkali) (d) Increase PIP and/or PEEP until MAP=17 cm H_2O (e) If Pao_2 <6·7 kPa or Pco_2 >7·3 kPa after 15 minutes	(a) Consider treating hypotension or extrapulmonary right to left shunting (for example, by infusion of plasma, blood, dopamine, tolazoline, or 1 mmol/kg alkali) (b) Increase PIP or PEEP or I:E ratio until MAP=17 cm H_2O (c) If Pao_2<6·7 kPa or Paco_2>7·3 kPa after 15 minutes
	Consider relaxing allocated protocol (a)–(e) Can be completed in 30 minutes if necessary	**Consider relaxing allocated protocol** (a)–(c) Can be completed in 30 minutes if necessary

FIO_2, fractional inspired oxygen; HMD, hyaline membrane disease; I:E, inspiratory:expiratory; MAP, mean airway pressure; Paco_2, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.

*Modified from Sedin[10]; **after 1985, if Paco_2 remained low and PIP could not be cut without reducing oxygenation, the rate was slowed, keeping inspiratory time ≤0·5 sec.

Archives of Disease in Childhood 1991; 66: 776–779

Factors associated with chronic lung disease in preterm infants

R W I Cooke

Abstract
Among 659 infants of 30 weeks' gestation or less born in a regional perinatal centre between 1983 and 1989, 195 were ventilated for four days or more and survived to 28 days, and 87 of these developed chronic lung disease. There was a sevenfold increase in the annual incidence of chronic lung disease over time. During the same period there were significant increases in the number of infants who survived, the incidence of septicaemia, and the use of parenteral lipid emulsions. Chronic lung disease was significantly associated with low birth weight, shorter gestation, duration of ventilation, vaginal delivery, sepsis, and the use of lipid. Respiratory and physiological measurements at 96 hours were significantly worse in infants who subsequently developed chronic lung disease. Initial logistic regression showed that gestation, arterial carbon dioxide tension ($PaCO_2$), and ventilation rate at 96 hours; and birth in 1988 or 1989, were independently associated with chronic lung disease, but when septicaemia and use of lipid during the first 21 days were included, only gestational age (odds ratio 0·64, 95% confidence interval (CI), 0·49 to 0·81 for each week) and use of lipid (odds ratio 8·1, 95% CI, 2·32 to 28·0) remained significantly associated with chronic lung disease.

The observed increase in incidence of chronic lung disease in this population was associated with earlier use of parenteral lipids in infants of very low gestation rather than with changes in population, survival, or ventilator treatment of respiratory distress syndrome.

ersey Regional
eonatal Intensive
are Unit,
iverpool Maternity
ospital, Liverpool
7 7BN

orrespondence to:
rofessor Cooke.

ccepted 16 April 1991

Since the introduction of mechanical ventilation for the treatment of severe respiratory distress syndrome in preterm infants, the main complication limiting successful outcome has been chronic lung disease. This is usually defined as oxygen dependence at 28 days of life in an infant with a history of mechanical ventilation during the first week of life and characteristic radiographic changes in the lung fields. First described by Northway *et al*,[1] it has variously been attributed to oxygen toxicity, barotrauma, infection, and the vulnerability of the lungs in very preterm infants.[2]

During recent years many centres have reported an increasing incidence of chronic lung disease, and the incidence varies considerably among centres. It has been suggested that the rising incidence is related to the survival of an increasingly vulnerable population of infants of lower gestational age who would previously have died. Differences in respiratory management have been suggested as one explanation for the variation in incidence among similar centres.[3] A considerable rise in the numbers of infants with chronic lung disease has recently been observed in the Mersey regional neonatal intensive care unit, and this study was initiated to see if this change could be explained by changes in the population alone, or whether factors such as changes in management or increased survival played a part.

able 1 Inborn infants of 30 weeks' gestation or less who were ventilated for at least four ays: condition at 28 days (n=260). Figures are expressed as number (%)

	1983	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*
ead	11 (31)	11 (31)	8 (25)	11 (24)	10 (34)	8 (20)	6 (14)
live breathing oxygen	4 (11)	8 (22)	10 (31)	10 (22)	6 (21)	22 (55)	27 (63)
live breathing air	20 (57)	17 (47)	14 (44)	24 (53)	13 (45)	10 (25)	10 (23)
otal	35	36	32	45	29	40	43

^{2} for trend=25·5, p<0·00001.

Patients and methods

Infants of 24 to 30 weeks' gestation admitted to the Mersey neonatal intensive care unit between 1 January 1983 and 31 December 1989 were included in the study if they were born in the hospital, were ventilated for at least the first four days of life, and survived to at least 28 days (table 1). Infants born at other hospitals and admitted later were not included because of incompleteness of early physiological data. Infants were considered to have chronic lung disease if they were oxygen dependent at 28 days, had received mechanical ventilation, and had characteristic radiographic changes.

Descriptive, respiratory, and physiological variables were abstracted from the clinical and intensive care records, which had been stored on microfiche. Descriptive variables included birth weight; gestation; sex; number of days ventilated; whether transferred to the centre in utero; use of pancuronium; use of parenteral lipid emulsions; singleton or multiple delivery; caesarean section; occurrence of pneumothorax, persistent ductus arteriosus, or septicaemia; and the presence of chronic lung disease. Persistent ductus arteriosus was defined as the presence of clinical signs sufficient to lead to a change in management such as fluid restriction, and septicaemia as a positive blood culture. Parenteral lipid emulsions (Intralipid 20%, Kabi-Vitrum) were given through peripheral or central lines at a rate of 5 ml/kg/day, increasing over four days to a maximum of 20 ml/kg/day. These variables were examined initially, together

Table 2 Changes in proportions of study infants (n=195) with septicaemia, receiving lipids, and requiring ventilation on day 10

	1983	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	χ^2 *for trend*	*p Value*
Septicaemia	11 (46)	14 (56)	17 (71)	24 (71)	14 (74)	26 (81)	27 (73)	7·4	0·006
Lipid used for <21 days	3 (13)	14 (56)	14 (58)	18 (53)	13 (68)	30 (94)	33 (89)	45·9	<0·0001
Ventilated at day 10	6 (25)	10 (40)	16 (67)	12 (35)	7 (37)	22 (69)	23 (62)	8·8	0·003
Total	24	25	24	34	19	32	37	—	—

with respiratory and physiological variables measured at 6, 48, and 96 hours of age according to year of birth, for significant trends to change with time (χ^2 for trend) (table 2). The same variables were then compared in infants with and without chronic lung disease (table 3), together with respiratory and physiological variables measured at 6, 48, and 96 hours of age (table 4). If a particular measurement had not been recorded exactly at one of the required times, the next recording was taken. All blood gas measurements were made in arterial samples and all blood pressure recordings were taken from catheters in the aorta or radial artery. Alveolar:arterial (A:a) ratios were computed from the blood gas measurements and the fractional inspiratory oxygen (FIO_2.)

The significance of differences was assessed with the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. The descriptive variables, the year of birth, and those respiratory and physiological variables that differed significantly between the two groups at the 5% level or less, were then entered in a logistic regression analysis (SPSS-X-Probit, Logit option[5]) and the regression coefficient and its standard error derived for each variable (table 5). The odds ratio and 95% confidence intervals (CI) were calculated where appropriate. Because the greater number of days spent being ventilated in the group with chronic lung disease was thought to be partly a result of chronic lung disease rather than a cause, this variable was not included in the analysis.

Table 3 Demographic variables and management in 195 infants with and without chronic lung disease. Figures are expressed as number (%) except where otherwise stated

	Infants without chronic lung disease (n=108)	*Infants with chronic lung disease (n=87)*	*p Value*
Median (range) weight (g)	1208 (612–1944)	903 (610–2000)	<0·00001
Median (range) gestation (weeks)	29 (24–30)	27 (24–30)	<0·00001
Multiple pregnancy	22 (20)	18 (21)	0·99
Caesarean section	66 (61)	36 (41)	0·003
Median (range) days ventilated	7 (4–50)	25 (4–300)	<0·00001
Ventilated day 10	22 (20)	74 (85)	<0·00001
Male	62 (57)	53 (61)	0·52
In utero transfer	72 (67)	53 (61)	0·87
Pancuronium	72 (67)	67 (77)	0·23
Lipid <21 days	43 (40)	82 (94)	<0·00001
Pneumothorax	28 (26)	30 (34)	0·25
Persistent ductus arteriosus	43 (40)	41 (47)	0·37
Septicaemia	61 (56)	72 (83)	0·00009

Table 5 Results of logistic regression with chronic lung disease as dependent variable

Independent variable	*Regression coefficient*	*Standard error*
Weight	0·015	0·143
Gestation*	−0·452	0·121
Vaginal delivery	0·262	0·302
Septicaemia	0·116	0·321
Lipid <21 days*	2·088	0·623
$PaCO_2$ at 96 hours	0·019	0·024
A:a ratio at 96 hours	−0·505	0·805
pH at 96 hours	−0·462	2·596
Ventilator rate at 96 hours	0·010	0·007
Year:		
1984	0·278	0·789
1985	−0·138	0·820
1986	−0·967	0·814
1987	−0·936	0·851
1988	0·113	0·815
1989	0·407	0·807

*p<0·001.

Table 4 Respiratory measurements at 6, 48, and 96 hours in 195 infants with and without chronic lung disease. Values are expressed as median (range)

	Time (hours)	*Infants without chronic lung disease (n=108)*		*Infants with chronic lung disease (n=87)*	
FIO_2	6	0·75	(0·21–1·00)	0·85	(0·21–1·00)
	48	0·70	(0·28–1·00)	0·75	(0·21–1·00)
	96	0·40	(0·21–1·00)	0·55	(0·21–1·00)
Ventilator rate/min	6	40	(0–100)	40	(6–100)
	48	57	(0–100)	55	(0–120)
	96*	30	(0–90)	40	(0–131)
Peak airway pressure (cm H_2O)	6	20	(0–45)	22	(15–44)
	48	20	(0–34)	22	(4–41)
	96	18	(0–25)	18	(0–32)
PaO_2 (kPa)	6	7·86	(3·07–23·50)	9·06	(3·07–34·70)
	48	8·40	(3·20–28·80)	8·53	(4·80–21·20)
	96	9·86	(4·00–23·05)	8·66	(4·27–19·20)
$PaCO_2$ (kPa)	6	5·07	(2·93–13·20)	5·07	(2·67–8·13)
	48	5·73	(3·07–10·00)	5·60	(2·67–10·90)
	96**	5·07	(2·13–9·73)	5·60	(2·53–9·06)
pH	6	7·36	(6·92–7·52)	7·34	(7·00–7·50)
	48	7·27	(6·99–7·46)	7·27	(7·01–7·48)
	96†	7·32	(6·99–7·60)	7·30	(7·15–7·42)
A:a ratio	6	0·143	(0·038–0·646)	0·147	(0·035–0·621)
	48	0·140	(0·038–0·506)	0·136	(0·059–0·680)
	96‡	0·283	(0·065–0·990)	0·210	(0·060–0·950)
Mean arterial blood pressure (mmHg)	6	36	(21–58)	34	(16–56)
	48	40	(25–60)	39	(23–59)
	96	45	(29–76)	42	(22–73)

*p=0·03, **p=0·002, †p=0·012, and ‡p=0·009.

Results

During the seven year period studied 659 infants of between 24 and 30 weeks' gestation were born in the hospital and admitted to the neonatal intensive care unit. Of these, 195 infants were ventilated for four or more days and survived to at least 28 days of life, and these form the study group. Eighty seven developed chronic lung disease as defined. There were no significant differences with time in the distribution of gestational age, birth weight, sex, incidence of caesarean section, multiple gestation, in utero transfer, or male sex, in the frequency of use of pancuronium, occurrence of pneumothorax or persistent ductus arteriosus, or in any of the physiological or respiratory variables. There was a sevenfold increase in the incidence of chronic lung disease (table 1), together with an increase in the incidence of septicaemia, in the use of lipid emulsions, and in the proportion of infants still being ventilated on day 10 (table 2).

The characteristics of the infants in the study group are shown in table 3, grouped according to whether they developed chronic lung disease or not. Those that did were lighter and less mature, were less likely to have been delivered by caesarean section, were ventilated longer, and were more likely to have received parenteral lipid during the first 21 days of life and to have had septicaemia. The respiratory and physiological variables are shown in table 4. Significant differences between infants with and without chronic lung disease were seen only at 96 hours when the ventilator rate, peak airway pressure, and arterial carbon dioxide tension (Paco$_2$) were higher, and the pH and A:a ratio were lower. When the descriptive variables, the year of birth, and those respiratory and physiological variables that differed significantly between the two groups were entered in a logistic regression with chronic lung disease as the dependent variable, only gestation, birth in 1988 or 1989, and Paco$_2$ and ventilator rate at 96 hours were independently associated with chronic lung disease. The inclusion of septicaemia as an independent variable left only gestational age and birth in 1988 and 1989 independently associated with chronic lung disease, and the inclusion of lipid use in the first 21 days left only gestational age (odds ratio 0·64, 95% CI 0·49 to 0·81, for each week) and use of lipid at <21 days (odds ratio 8·1, 95% CI 2·32 to 28·0) with significant associations (table 5).

Discussion

Neonatal intensive care has been described as a continuing experiment, and certainly many of the factors that may affect outcome either for good or ill are constantly changing. When an adverse outcome such as chronic lung disease in preterm survivors of intensive care is seen to increase, it is often difficult to find out whether the change is the result of changes in the population served, in survival, or in factors relating to techniques of management. Chronic lung disease in inborn infants of 30 weeks' gestation or less and ventilated for four days or longer has apparently risen sevenfold during a seven year period, and mainly in the last two years. When demographic variables significantly associated with chronic lung disease in this group were taken into account in the logistic regression the years 1988 and 1989 remained significantly associated with chronic lung disease, suggesting that factors other than demographic changes were responsible for the observed change in incidence of chronic lung disease.

'able 6 *Numbers of neonatal survivors who received parenteral lipid, and time of start by ear of birth*

	1983	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*
–9 days	1	0	1	1	5	19	26
0–21 days	2	14	13	17	8	11	7
)ver 21 days or never	20	11	10	16	6	2	4
'otal	24	25	24	34	19	32	37

^{2} for trend 72·6, $p<0·00001$.

Though there was a clear trend to increased neonatal survival in this high risk group (table 1), this cannot account fully for the observed increase in chronic lung disease. If this were so, the numbers of neonatal deaths together with the number of infants in oxygen at 28 days should form a similar proportion of the total population in each year. As seen in table 1, this proportion increased during the seven year period from 42% to 77%. A number of respiratory and physiological measurements made at 96 hours of age were significantly associated with chronic lung disease. In the logistic regression only Paco$_2$ and respiratory rate at 96 hours remained significantly associated with chronic lung disease before septicaemia and lipid use were taken into account. The improved survival of the very immature that has clearly occurred, especially in the last two years of this study, could have been the result of a more intensive attitude to ventilation of this group of infants. Kraybill *et al* suggested that the observed variation in the incidence of chronic lung disease among a number of neonatal intensive care units in the United States was attributable to differences in the intensity of mechanical ventilation, as shown by the lower Paco$_2$ at 48 hours of age reported from centres with higher rates of chronic lung disease.[4] The differences seen in this study were in the opposite direction, implying that infants who developed chronic lung disease were sicker at 96 hours of age rather than overventilated at 48 hours. The lack of an independent association between respiratory variables and the occurrence of chronic lung disease as previously shown suggests that while methods of ventilation may account for differences in chronic lung disease rates among centres, they do not explain the recent increases in incidence within centres.

The increase in the incidence of septicaemia was almost entirely related to an increase in coagulase negative staphylococcal infection. Septicaemia, though strongly associated with chronic lung disease in the univariate analysis, failed to achieve independent association in the logistic regression model after lipid use had been allowed for. Though septicaemia could be causally associated with chronic lung disease, it is also probable that infants who developed chronic lung disease were more prone to infection. The use of lipid emulsions during the first 21 days of life was strongly associated with chronic lung disease, and when it was entered in the regression model it was the only factor to account for the higher incidence of chronic lung disease in 1988 and 1989.

The association between chronic lung disease and the use of lipid could be explained by lipid being given mainly to sicker infants. Examination of lipid prescription in this group during the study period, however, showed a pronounced change in the age at which it was started. In particular, much earlier use of lipid was made in the last two years (table 6) in the absence of any significant change in the early severity of illness as measured by the respiratory and physiological variables. The use of lipid emulsions in sick preterm infants has been associated with higher rates of coagulase negative staphylococcal sepsis,[6] as was the case in this study, when 81% of infants receiving lipid became septicaemic, compared with 40% of those who did not ($p<0\cdot0001$). Giving lipid to preterm infants is associated with an excess generation of free radical induced lipid peroxidation, and thromboxane production,[7] and free radical induced lung damage has been proposed as a factor in the genesis of chronic lung disease.[8] Recently a small clinical trial of lipid given for five days to preterm infants undergoing intensive care showed a significant excess of chronic lung disease and retinopathy in treated infants compared with controls.[9]

The earlier use of parenteral lipid solutions on this unit was introduced because of concern over poor growth in these sick, very low birthweight infants when amino acids and dextrose/electrolyte solutions alone were used for nutrition. It is likely that this exposed a large number of infants in the earlier stages of hyaline membrane disease to lipid, when they were most vulnerable to lung injury, and that this change in practice accounted for the increase in chronic lung disease seen in recent years.

Until further evidence is available, the use of parenteral lipid emulsions should be restricted to older preterm infants, or to those without respiratory symptoms. In sick preterm infants any theoretical gains made from early parenteral lipid infusion are outweighed by an increase in the incidence of chronic lung disease in the following weeks and months.

1 Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline membrane disease; bronchopulmonary dysplasia. *N Engl J Med* 1967;**276**: 357–8.

2 Boynton BR. Epidemiology of bronchopulmonary dysplasia. In: Merritt TA, Northway WH, Boynton BR, eds. *Bronchopulmonary dysplasia. Contemporary issues in fetal and neonatal medicine.* No 4. Boston: Blackwell Scientific Publications, 1988:19–32.

3 Avery ME, Tooley WH, Keller JB. Is chronic lung disease in low birthweight infants preventable? A survey of eight centres. *Pediatrics* 1987;**79**:26–30.

4 Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birthweights of 751 to 1000 grams. *J Pediatr* 1989;**115**:115–20.

5 *SPSS-X users guide.* 3rd Ed. Chicago: SPSS Inc, 1988.

6 Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteraemia in neonatal intensive care units. *N Engl J Med* 1990;**323**: 301–8.

7 Pereira GR, Fox WW, Stanley CA, Barker L, Schwartz JG. Decreased oxygenation and hyperlipemia during intravenous fat infusions in premature infants. *Pediatrics* 1980;**66**:26–30.

8 Saugstad OD. Hypoxanthine as an indicator of hypoxia; its role in health and disease through free-radical production. *Pediatr Res* 1988;**23**:143–50.

9 Hammerman C, Aramburo MJ. Decreased lipid intake reduces morbidity in sick premature neonates. *J Pediatr* 1988;**113**:1083–8.

Archives of Disease in Childhood 1991; **66:** 780–782

Phosphorus metabolites in the human placenta estimated in vivo by magnetic resonance spectroscopy

A M Weindling, R D Griffiths, A S Garden, P A Martin, R H T Edwards

Abstract

Normal human placental metabolism has been studied in vivo by image localised ^{31}P magnetic resonance spectroscopy in 13 women with anterior placentas; five, however, were too fat for useful spectral signals to be obtained. Magnetic resonance spectra of good quality which were considered to have arisen from the placenta were obtained from seven women with uncomplicated pregnancies (median gestational age 35 weeks, range 28–39). One other woman had a twin pregnancy in which one fetus had died a few days before. The phosphodiester signal from the placenta of the dead fetus was outside the 95% confidence intervals for normal placentas, suggesting that this technique may potentially be useful in the assessment of placental function.

The ability to assess fetal wellbeing reliably is essential for making informed decisions about the management of the fetus that is considered to be at risk. The ideal method should be safe, non-invasive, and capable of providing information in normal as well as abnormal pregnancies. Indirect methods, such as Doppler blood flow studies, are neither specific nor sensitive enough to diagnose a hypoxic fetus accurately. Direct methods, such as cordocentesis, are invasive and risky.

Magnetic resonance (MR) spectroscopy, although expensive, has the potential for providing information about fetal wellbeing.[1] Earlier in vitro work suggested that MR could have a role in the study of placental disorders.[2]

Following a brief preliminary report,[3] we present the first observations of human placental metabolism assessed non-invasively by ^{31}P MR spectroscopy.

Methods

We used a General Electric Signa MR system with a field strength of 1·5 tesla. Pregnant women were recruited from the antenatal clinic and ward. Each subject lay in a lateral position to avoid aortocaval compression. As a single examination lasted up to 1·5 hours, foam padding was used to make her as comfortable as possible. Sixty three examinations have been made to image fetuses; none has had to be stopped because of physical discomfort and only one because of claustrophobia.

LOCALISATION OF THE FETUS AND PLACENTA

The fetus was imaged using a fast scan technique that has previously been described.[4] The precise position of the placenta in relation to the anterior abdominal wall, the uterus, and the fetus was established in at least two orthogonal views using the following settings: repetition time 25 msec, echo delay time 12 msec, and a flip angle of 10°.

MAGNETIC RESONANCE SPECTROSCOPY

An 11 cm diameter transmit and receive surface coil was used to generate a ^{31}P spectrum from the placenta. The exact position of the surface coil on the anterior abdominal wall was confirmed by a small glycerol phantom built into the coil, which could be seen on the fast scan MR images.

The size and position of the coil were such that, from the images obtained, placental tissue could be seen extending at least as far as one coil's radius from the outer edge of the coil. The image based spectroscopy protocol, one dimensional chemical shift imaging (1D-CSI), was used to define contiguous slices 10 mm thick and parallel to the surface coil in the orthogonal plane.[5]

The sensitive volume of our surface coil was checked by conventional imaging of a phantom, which was constructed to subject the coil to identical operating conditions (for example, coil loading) as those encountered for a pregnant woman. The radio frequency pulse power was chosen so that the sensitive volume produced was shaped like a shallow dome. At 4 cm depth—the depth at which the placenta was encountered—the volume was roughly a flat disk 7 cm in diameter. Together with the image based spectroscopy protocol (1D-CSI, repetition time 1 second, and 16 excitations with 128 phase encoding steps), this technique, which produced 1 cm thick slices parallel to the plane of the coil, gave a sensitive volume of about 38 ml.

The number of phase encoding steps was unusual and was used for two reasons. Firstly, our computer software worked more efficiently on multiples of 128. Secondly, the number of phase encoding steps determined the number of data points in the spatial direction; the more such points there were, the better the spatial resolution.

Previous reproducibility studies at this centre using an identical technique to study the spleen

University of Liverpool,
PO Box 47,
Liverpool L69 3BX,
Department of
Child Health
A M Weindling

Department of Medicine
R D Griffiths
R H T Edwards

Department of Obstetrics and Gynaecology
A S Garden

Magnetic Resonance Research Centre
P A Martin

Correspondence to:
Dr Weindling.

Accepted 7 January 1991

found a coefficient of variation of metabolite ratios of between 2 and 14%.[6]

A study was considered satisfactory if at least two contiguous 1 cm slices could be localised within the placenta on both the axial and sagittal images. The MR signal that was analysed was obtained at 4 cm depth from the coil. Proton 1D-CSI spectra were collected to confirm localisation and for additional chemical shift reference. Spectra were processed with a Sun work station running the General Electric SA/GE spectroscopy software. Automated curve fitting was done with the Marquardt-Levenburg nonlinear least squares algorithm.

Each metabolite was expressed as a fraction of the total phosphorus signal. No attempt was made to correct for partial saturation effects which were invariably present because of the short repetition time used.

PATIENTS

Seven normal pregnant women (median gestational age 35 weeks, range 28–39) were studied. One other woman with a twin pregnancy in which one of the fetuses had died a few days before was also studied. These studies were approved by the ethics committee of this health authority, and were carried out within the guidelines of the National Radiological Protection Board of the United Kingdom.[7]

Results

It was possible to differentiate the spectra that originated from the anterior abdominal wall, the placenta and uterine wall, and the placenta alone at 4 cm depth (fig 1). The spectrum from the placenta of the dead fetus is shown in fig 2.

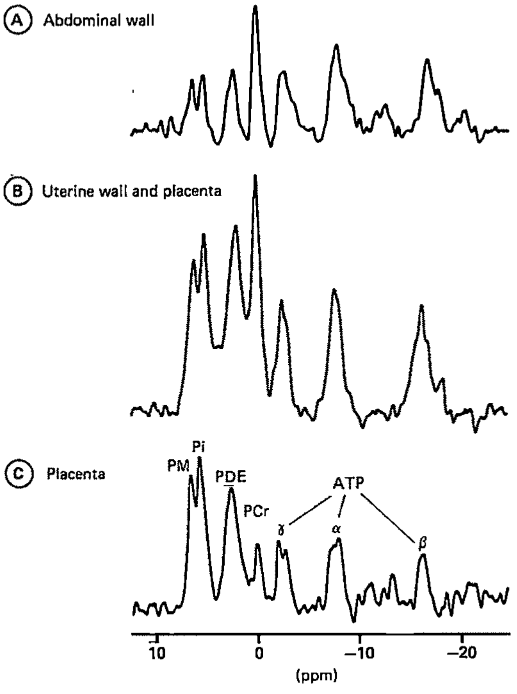


Figure 1 Image localised ^{31}P spectrum obtained with one dimensional chemical shift imaging from (A) the abdominal wall, (B) uterine wall and placenta, and (C) human placenta in vivo at 35 weeks' gestation. The placental spectrum was obtained from a slice 4 cm deep to the surface coil. PM, phosphomonoesters; Pi, inorganic phosphate; PCr, phosphocreatine; and PDE, phosphodiesters.

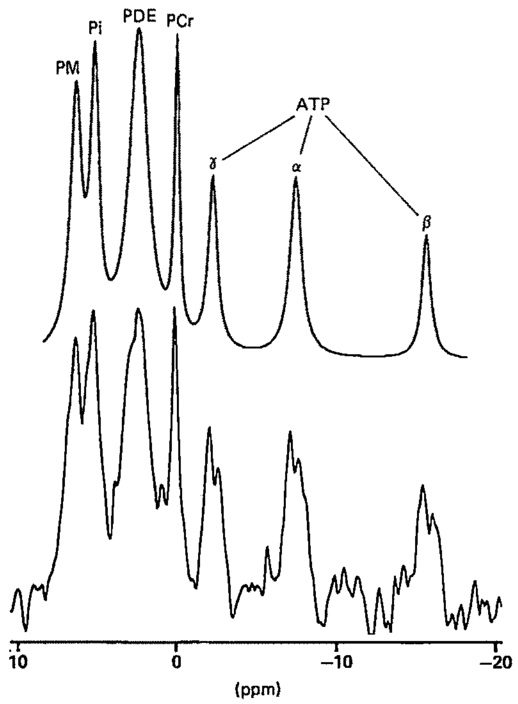


Figure 2 ^{31}P spectrum from the placenta of the dead fetus. The raw signal is shown in the lower panel, with the smoothed signal generated by the computer assisted curve fitting program in the upper panel. PM, phosphomonoesters; Pi, inorganic phosphate; PCr, phosphocreatine; and PDE, phosphodiesters.

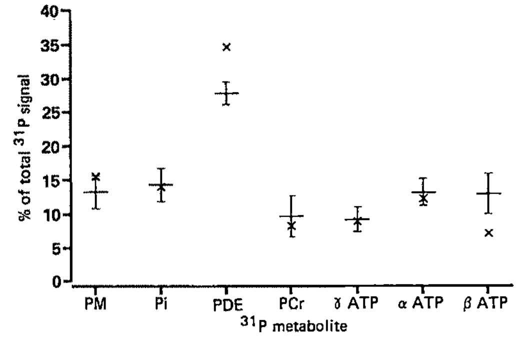


Figure 3 Quantitative ^{31}P metabolite data from seven uncomplicated pregnancies expressed as a proportion of the total phosphorus signal; bars indicate mean (95% confidence intervals). The results obtained from the placenta of the dead fetus are indicated separately (X). PM, phosphomonoesters; Pi, inorganic phosphate; PCr, phosphocreatine; and PDE, phosphodiesters.

Studies of five other women were abandoned because they were fatter, and as a result their placentas were deeper than the 4–5 cm required for optimal collection of signals.

The data from each of the seven normal subjects were combined to give a mean value with 95% confidence intervals (CI). The phosphodiester signals from the placenta of the dead fetus fell outside the 95% CI (fig 3); although the βATP signal from the dead fetus was also low, the signal:noise ratio from this relatively small signal was poor, and we are therefore reluctant to place too much significance on this observation.

Discussion

These studies have shown that it is possible to obtain magnetic resonance spectra from anteriorly placed placentas. There was no evidence of any systematic change in signal with gestation, and one reason for this is that the placenta is functionally mature by 28 weeks.

When placental function was grossly deranged, however (in the case of the intrauterine death), possible breakdown products were visible. Phosphomonoesters and phosphodiesters are representative of phospholipid metabolism. Their major constituents are the precursors of membrane constituents—that is, phosphorylethanolamine (a precursor of phosphatidylethanolamine) and phosphorylcholine (a precursor of phosphatidylcholine). Phosphomonoester signals might be expected to increase during early pregnancy and cell growth, and to decline when the placenta matures or earlier if growth ceases. The sugar phosphates, notably 2, 3-diphosphoglycerate in red blood cells, also contribute to the phosphomonoester signal. The phosphodiester resonance arises from contributions from glycerophosphorylethanolamine and glycerophosphorylcholine, which are the degradation products of phospholipids and myelin.

As predicted by Dawson *et al*,[8] the ability to detect in vivo large resonances from inorganic phosphorus and the products of phospholipid synthesis and catabolism seems to offer the opportunity to study placental function and its disorders. The relatively larger amounts of phosphodiesters that were observed in the case of the placenta of the dead fetus were much what might have been expected in theory.

We are aware that our method of localising to a slice allowed some contamination of the signal, both from neighbouring tissues and from non-placental tissue at the ends of the slice. This was in part restricted by the sensitivity of the surface coil, but there was inevitably some contamination (probably less than 10%) from myometrium or abdominal wall and this may have accounted for the fairly large phosphocreatine signal. The enzyme creatine kinase has been described in placental tissue and small amounts of phosphocreatine are present on placental extract analysis.[9] The absence of phosphocreatine from in vitro studies may have been the result of hydrolysis. The much larger phosphodiester signal is more interesting, and cannot be accounted for by myometrial contamination; the finding is in contrast with in vitro studies that showed a low content.[10] One explanation has come from studies of hepatic phosphodiester metabolism by Bates *et al.*[11] They suggested that a signal caused by the phospholipid component of the membranes is seen at the lower field strength at which in vivo studies are carried out; this is lost at the higher fields used in the in vitro analyses because of chemical shift anisotropy in an underlying broad hump.[11]

Caution must therefore be exercised in predicting possible in vivo changes from in vitro studies for two reasons. Firstly, because of the different field strengths. Secondly, because of the rapid reduction in ATP concentration in the human placenta after delivery, which was shown by Carroll and Young, who suggested that biochemical deterioration may occur within 30 seconds of delivery.[12]

The safety of any technique used in pregnancy is of paramount importance. Safety aspects of this technique were considered carefully. National Radiology Protection Board guidelines relate to exposure to radio frequency power. A conventional magnetic resonance image is one tenth of that specified in the guidelines.[7] The fast scan imaging technique used in these studies required one hundredth of the energy of conventional images. Magnetic resonance spectroscopy required one tenth of the energy of fast scan images, that is one ten-thousandth of that specificed in the guidelines. Cell cultures and animal studies have also been done to assess the safety of MR, and studies of pregnant mice showed no differences in litter numbers or growth rates in animals exposed to MR compared with controls.[12] Follow up studies of patients and volunteers who have undergone imaging also failed to show any hazards.[13]

This technique is still some way from being clinically useful. Improved coil design to provide a more homogeneous transmitting field will improve localisation and allow comparison of slices recorded at different depths.

We gratefully acknowledge support from Action Research for the Crippled Child.

1 Griffiths RD, Edwards RHT. The biomedical applications of spectroscopy and spectrally resolved imaging. In: Wehrli F, Kneeland WP, Shaw D, eds. *Principles and applications of biomedical magnetic resonance imaging*. USA: VCH Publishers, 1988:521–51.

2 Noyszewski EA, Raman J, Trupin SR, McFarlin BL, Dawson MJ. Phosphorus 31 nuclear magnetic resonance examination of female reproductive tissues. *Am J Obstet Gynecol* 1989;**161**:282–8.

3 Griffiths RD, Weindling AM, Garden AS, Martin PA, Edwards RHT. Image guided ^{31}P MR spectroscopy of the human placenta. *Society of Magnetic Resonance Medicine Abstracts* 1989;**2**:582.

4 Garden AS, Griffiths RD, Weindling AM, Martin PA. Fast scan magnetic resonance imaging in fetal visualisation. *Am J Obstet Gynecol* (in press).

5 Glayzer GM, Smith SR, Chevenert TL, Martin PA, Stevens AN, Edwards RHT. Image localized ^{31}P magnetic resonance spectroscopy of the human liver. *Nuclear Magnetic Resonance in Biomedicine* 1989;**1**:184–9.

6 Smith SR, Martin PA, Davies JM, Edwards RHT. Characterisation of the spleen by in vivo image guided 31P magnetic resonance spectroscopy. *Nuclear Magnetic Resonance in Biomedicine* 1989;**2**:172–8.

7 National Radiological Protection Board. Revised guide-lines on acceptable limits of exposure during NMR clinical imaging. *Br J Radiol* 1981;**138**:159–60.

8 Dawson MJ, McFarlane DK, McFarlin BL, Noyszewski EA, Trupin SR. The biochemistry of female reproductive tissues studied by 31 phosphorus nuclear magnetic resonance spectroscopy: effects of pregnancy, hormonal manipulation, and disease. *Biol Reprod* 1988;**38**:31–8.

9 Kay HH, Gordon JD, Ribeiro AA, Spicer LD. ^{31}P NMR spectroscopy studies of human placenta and placental extracts. *Society of Magnetic Resonance Medicine Abstracts* 1988;**1**:475.

10 Robbie D, Foster MA. Pulsed magnetic field exposure during pregnancy and implications for NMR foetal imaging: a study with mice. *Magnetic Resonance Imaging* 1985;**3**:231–4.

11 Bates TE, Williams SR, Gadian DG. Hepatic phosphodiester signals in vivo: the importance of field strength. *Society of Magnetic Resonance Medicine Abstracts* 1989;**2**:553.

12 Carroll MJ, Young M. Observations on the energy and redox state and protein synthetic rate in animal and human placentas. *J Perinat Med* 1987;**15**:21–30.

13 Reid A, Smith FW, Hutchison JMS. Nuclear magnetic resonance imaging and its safety implications: follow up of 181 patients. *Br J Radiol* 1982;**55**:784–6.

Temperature instability during nursing procedures in preterm neonates

Q Mok, C A Bass, D A Ducker, N McIntosh

epartment of
hild Health,
t George's Hospital,
lackshaw Road,
ondon SW17 0RE
Mok
A Bass
A Ducker
McIntosh

orrespondence to:
r Mok.

ccepted 14 January 1991

Abstract

The temperature changes associated with total care nursing procedures were studied on 249 occasions during the first week of life in 25 preterm infants weighing less than 1500 g, 16 of whom weighed less than 1100 g. Large drops in both central and peripheral temperature occurred, with widening of the central-peripheral temperature gap. Recovery of the temperature after the total care procedure took up to two hours.

These routine nursing procedures are carried out every four to six hours. They cause an important alteration in the environmental temperature with consequent thermal stress to the infants that may influence ultimate outcome.

There is a narrow range of ambient temperature within which the metabolic rate and oxygen demand of neonates are minimal.[1] This neutral thermal environment varies with an infant's body weight, age, and amount of clothing,[2 3] and is important because babies managed at environmental temperatures outside this range may grow less adequately,[4] and be at risk of increased mortality and morbidity.[5–7]

Without outside help the preterm baby behaves like a classic poikilotherm, its temperature reflecting that of its surroundings.[8 9] The provision of a neutral thermal environment with incubators and overhead heaters is an important feature of neonatal intensive care. In 1985 we reported temperature fluctuations that occurred during the handling of babies,[10] and showed that they were more pronounced when the incubator was used in a servo controlled temperature mode.[11] The aim of the present study was to monitor the degree and importance of these temperature changes during handling.

Patients and methods

Temperature recordings were collected from 25 very low birthweight babies (less than 1500 g) admitted to the neonatal intensive care unit at this hospital. The infants were subdivided into those weighing above and below 1100 g, as infants weighing less than 1100 g (n=16) were nursed in humidified incubators for the first 14 days. The babies were routinely nursed naked and covered by a single layer of bubble plastic in closed incubators the air in which was controlled at the temperature of the infant's neutral thermal environment.[11] The temperature of the nursery was set at 28°C and the humidity at 40%.

Total care nursing procedures that were carried out during the first week of life were monitored. These consisted of mouth care, measurement of axillary temperature, nappy change, turning, heel pricking for measurement of blood glucose concentration, and rotation of transcutaneous probe sites. If the infant was ventilated, physiotherapy and endotracheal tube suction would often be included. This routine, performed four to six hourly, took about 20 minutes to complete but could vary from 15 to 45 minutes, depending on the nurse and the tasks required. Temperature probes were attached to the abdominal skin and the sole of the foot to measure core and peripheral temperatures, respectively. These measurements were recorded continuously by Simonsen and Weel 8000 series monitors and were fed into the MARY neonatal monitoring system installed in the unit.[12] This system (Meadowbank Medical Systems Limited) can record up to 16 channels of physiological and environmental data from each intensive care cot. Data were obtained every second, averaged every minute, and stored on the hard disk of the host computer.

Results

The birth weights of the babies ranged from 510 to 1500 g (median 920). The babies were born at gestational ages ranging from 24 to 31 weeks (median 27). The temperature changes from a total of 249 total care procedures carried out during the first week of life were analysed. Figure 1 shows typical graphs of core and peripheral temperature fluctuations during total care procedures obtained from four of the babies during the study. There is generally a temperature gap reflecting the higher central temperature compared with the extremities. At the end of each total care procedure there was an obvious fall in both central and peripheral temperature in all babies. The peripheral temperature fell by a greater degree after total care such that the central-peripheral temperature gap widened. Recovery to the temperature before the procedure was gradual and could take as long as two hours.

The data obtained from the 249 procedures on the 25 babies are shown in the table. The central temperature fell by a mean of 0·7°C (range 0·0–1·7) and the peripheral temperature by 1·3°C (range 0·2–3·0). The temperature gap widened by an average of 0·6°C (range 0·0–2·7) after total care procedures. The lowest central temperature recorded was 34·8°C in a baby of 26 weeks' gestation who weighed 800 g, and the lowest peripheral temperature recorded was 32·6°C in a baby of 24 weeks' gestation who weighed 770 g. In one infant the temperature gap increased from 0·3°C at the start of a procedure to 3·0°C at the end.

Figure 2 shows the association between central and peripheral temperature changes and weight. Among the babies weighing <1100 g (those nursed in humidified incubators) there is a negative correlation between the fall in temperature and birth weight (fig 2A). This correlation was highly significant for the peripheral ($r=-0\cdot868$, $p<0\cdot0001$) but not for central temperature changes ($r=-0\cdot437$,

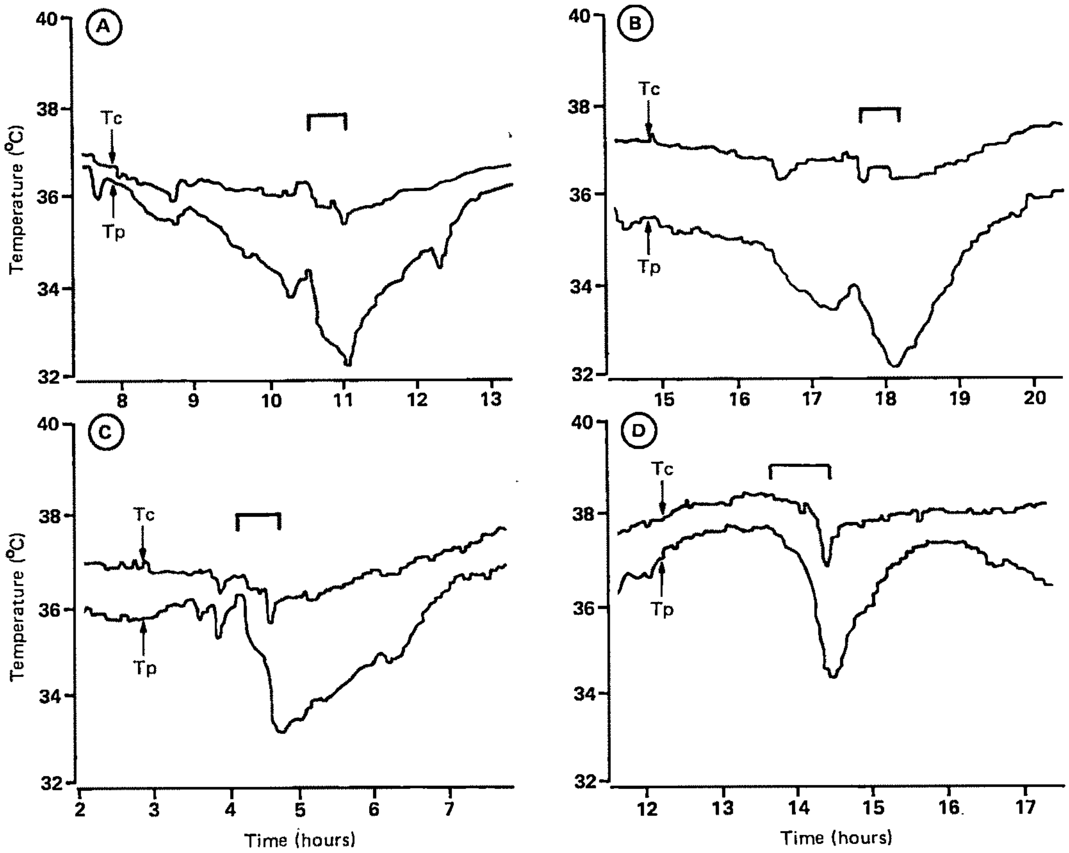


Figure 1 Examples of graphs obtained from different babies during total care procedures showing temperature fluctuations with time. In each graph the upper (Tc) and lower (Tp) trace indicates the central and peripheral temperatures respectively. Periods of total care are indicated by ┌──┐. *The babies' gestational ages, birthweights, and times of recording, respectively, were: (A) 31 weeks, 1500 g, day 5; (B) 28 weeks, 920 g, day 2; (C) 24 weeks, 770 g, day 3; and (D) 27 weeks, 1000 g, day 7.*

Details of 25 babies. Each temperature value is the mean of a series of total care procedures for each baby

Case No	*Gestation (weeks)*	*Weight (g)*	*No of procedures*	*Central temperature (°C)*			*Peripheral temperature (°C)*			*Central-peripheral difference (°C)*
				Before total care procedure	*After total care procedure*	*Difference*	*Before total care procedure*	*After total care procedure*	*Difference*	
1	27	510	17	37·7	36·8	0·9	36·9	34·9	2·0	1·1
2	24	630	7	37·5	37·1	0·4	36·3	34·6	1·7	1·3
3	26	640	11	37·6	36·4	1·2	36·7	34·8	1·9	0·7
4	24	770	8	37·8	37·1	0·7	36·6	34·7	1·9	1·2
5	27	790	17	37·7	36·7	1·0	36·9	35·4	1·5	0·5
6	26	800	6	37·2	36·3	0·9	36·3	35·1	1·2	0·3
7	28	820	15	36·9	36·2	0·7	36·4	35·0	1·4	0·7
8	28	820	5	37·5	37·1	0·4	36·3	34·9	1·4	1·0
9	26	850	11	37·3	36·8	0·5	36·4	34·9	1·5	1·0
10	28	870	3	37·9	37·1	0·8	36·3	35·5	0·8	0·0
11	27	890	6	36·9	36·1	0·8	36·1	35·0	1·1	0·3
12	28	900	16	37·0	36·3	0·7	36·1	34·8	1·3	0·6
13	28	920	9	37·3	36·7	0·6	36·5	35·5	1·0	0·4
14	27	1000	20	37·9	37·4	0·5	36·4	35·4	1·0	0·5
15	26	1020	9	38·1	37·5	0·6	36·5	35·5	1·0	0·4
16	27	1060	8	37·5	37·0	0·5	36·5	35·7	0·8	0·3
17	28	1170	9	36·8	36·1	0·7	35·9	34·8	1·1	0·4
18	28	1200	6	37·1	36·3	0·8	36·6	35·3	1·3	0·5
19	29	1270	14	36·9	36·4	0·5	36·1	35·2	0·9	0·4
20	28	1280	4	36·9	36·2	0·7	36·6	35·3	1·3	0·6
21	30	1310	5	38·0	37·4	0·6	36·7	35·4	1·3	0·7
22	31	1350	4	37·6	37·1	0·5	36·8	35·5	1·3	0·8
23	27	1385	14	37·0	36·4	0·6	35·5	34·5	1·0	0·4
24	29	1410	13	37·3	36·8	0·5	36·1	34·9	1·2	0·7
25	31	1500	12	37·3	36·4	0·9	36·2	34·5	1·7	0·8

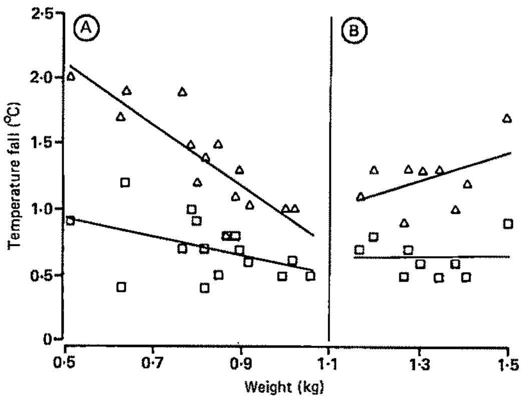


Figure 2 The association between central (squares) and peripheral (triangles) temperature changes with weight for babies (A) <1100 g and (B) ≥1100 g. A linear regression best fit line was calculated for each group; only the peripheral temperature drop in babies <1100 g was significant (p<0·0001).

p=0·087). In babies who weighed 1100 g or more, and who were nursed in non-humidified incubators (fig 2B), neither the central (r=0·036, p=0·889) nor the peripheral (r=0·488, p=0·181) temperature changes were significantly correlated with weight. There was no significant correlation between the temperature changes and gestational age.

Discussion

Heat is dissipated to the environment by radiation, convection, evaporation, and conduction, although heat loss from conduction is negligible from an infant managed in the neonatal intensive care unit. This study has shown that there is a significant temperature instability during routine total care nursing procedures. The change in temperature is often substantial—as much as 2·4°C centrally and 3·0°C peripherally—with slow recovery to normal.

Previous work showed that heat losses are more pronounced for preterm compared with term infants because of the relatively large body surface areas, poor fat insulation, thin epidermal layers, and increased peripheral blood flow in premature babies. The immature homoeostatic reflexes for maintaining body temperature in these infants also contribute to the fall in temperature and the slow recovery, as it has been shown that preterm babies are unable to increase heat producion to any appreciable extent.[8 9] These factors account for the higher heat loss, most notable in the periphery, in the lighter babies in our study. Heat loss would probably be more severe if these babies had not been incubated under humidified conditions in which heat loss by evaporation was minimal. The greater temperature drop in some of the heavier babies may be the result of higher heat loss by evaporation in non-humidified incubators.

Despite our attempts to maintain babies within the ideal thermal environment, there was an unavoidable fall in incubator temperature and humidity when portholes were opened for nursing care. Although we did not continuously monitor details of the incubator air temperature and humidity, it has previously been shown that incubator temperatures inevitably fall when the portholes or doors are opened.[13] In the small, sick infants in this study this led to a drop in the infants' temperature which only regained the normal values after about two hours.

In full term infants, hypothermia leads to an increase in the metabolic rate (and therefore oxygen demand) as the infant attempts to generate heat to regain normal temperatures.[14 15] In preterm infants with respiratory problems this may result in increased oxygen demand in a neonate whose oxygen requirements are already raised. This increased metabolic rate can cause acidosis, hypoglycaemia, and poor weight gain,[4] and if the baby already has respiratory difficulties, it may contribute to respiratory failure. Sauer *et al* reported that in preterm infants changes in body temperature are not always accompanied by increased oxygen consumption[3]; they redefined the neutral thermal environment as 'the ambient temperature at which the core temperature of the infant at rest is between 36·7 and 37·3°C and the core and mean skin temperatures are changing less than 0·2 and 0·3°C/hour, respectively'. During the total care nursing procedures, this neutral thermal environment was obviously disturbed and did not recover for some time. We have no information from our study about whether the temperature was regained by an increase in metabolic rate or by a decrease in the rate of heat loss to the surroundings (by a reduction in the gradient from the baby to incubator) thus allowing the heat generated by the babies' stable metabolic rate to accumulate.

It is our routine practice to monitor the peripheral and central temperatures of all preterm and low birthweight babies admitted to our unit. This is done by a graphical display at the cotside (fig 1). Close attention can be given to monitoring temperature changes during total care and other nursing and medical procedures. The procedures have now been modified to minimise fluctuations in temperature. For small babies the nurses increase the incubator temperature by one degree before their total care routine, and try to do the various tasks as quickly as possible, keeping a close watch on the monitor screen during the process. The visual feedback given by the computer as the procedure is carried out is important in reducing the thermal instability and possibly the thermal stress and metabolic demands on the baby.

We thank the nurses for their cooperation in this study, in particular for the care of patients and entry of the data.

1 Hey EN. Thermal neutrality. *Br Med Bull* 1975;31:69–74.
2 Hey EN, Katz G. The optimum thermal environment for naked babies. *Arch Dis Child* 1970;45:328–34.
3 Sauer PJJ, Dane HJ, Visser HKA. New standards for neutral thermal environment of healthy very low birthweight infants in week one of life. *Arch Dis Child* 1984;59:18–22.
4 Glass L, Silverman WA, Sinclair JC. Effect of thermal environment on cold resistance and growth of small infants after the first week of life. *Pediatrics* 1968;41:1033–46.
5 Buetow KC, Klein SW. Effect of maintenance of 'normal' skin temperature on survival of infants of low birth weight. *Pediatrics* 1964;34:163–9.
6 Silverman WA, Fertig JW, Berger AP. The influence of the

thermal environment upon the survival of newly born premature infants. *Pediatrics* 1958;22:876–86.

7 Day RL, Caliguiri L, Kamenski C, Ehrlich F. Body temperature and survival of premature infants. *Pediatrics* 1964;**34:** 171–81.

8 Bruck K. Temperature regulation in the newborn infant. *Biol Neonate* 1961;3:65.

9 Wheldon AE, Hull D. Incubation of very immature infants. *Arch Dis Child* 1983;**58**:504–8.

10 Ducker DA, Lyon AJ, Ross Russell R, Bass CA, McIntosh N. Incubator temperature control: effects on the very low birthweight infant. *Arch Dis Child* 1985;**60**:902–7.

11 Ducker DA, Lyon AJ, Wheeler KA, McIntosh N, Bass CA. Temperature variability of very low birthweight infants nursed in infant servo controlled incubators. In: Rolfe P, ed. *Neonatal physiological measurements*. Proceedings of the Second International Conference on Fetal and Neonatal Physiological Measurements. London: Butterworth, 1984:13–20.

12 McIntosh N, Ducker DA, Bass CA. MARY—a computerised neonatal cot monitoring system. *Intensive Therapy and Clinical Monitoring* 1989;**10**:272–82.

13 Ahlgren EW. Environmental control of the neonate receiving intensive care. *Int Anesthesiol Clin* 1974;**12**:173–215.

14 Scopes JW, Ahmed J. Minimal rates of oxygen consumption in sick and premature newborn infants. *Arch Dis Child* 1966;**41**:407–16.

15 Bell EF, Gray JC, Weinstein WR, Oh W. The effects of thermal environment on heat balance and insensible water loss in low birthweight infants. *J Pediatr* 1980;**96**:452–9.

rchives of Disease in Childhood 1991; **66:** 787–792

Site of upper airway obstruction in preterm infants with problematical apnoea

Nigel R Ruggins, A D Milner

epartment of
hild Health,
niversity Hospital,
ottingham
igel R Ruggins
D Milner

rrespondence to:
r Nigel R Ruggins,
hildren's Respiratory Unit,
niversity Hospital,
ueen's Medical Centre,
ottingham NG7 2UH.

ccepted 15 January 1991

Abstract

Airway obstruction is an important factor predisposing to the development of apnoea in preterm infants. An ultrafine fibreoptic scope was used to examine the upper airway of 12 preterm infants with recurrent problematical apnoea. Continuous visualisation of the airway was possible and recorded on to videotape together with simultaneous cardiorespiratory monitoring to detect apnoeic episodes in 12 infants studied. In seven infants obstruction was observed at laryngeal level with the arytenoid masses and aryepiglottic folds closing across the vocal cords. This was not only observed in obstructive apnoea but also during mixed apnoea in periods where no respiratory effort was detectable and again in apparently pure central apnoea. The findings confirm the larynx as an anatomical site of upper airway obstruction. They agree with other indirect methods of assessing airway patency that obstruction has an important role in the pathophysiology of apnoea of prematurity.

It is becoming recognised that obstruction of the upper airway is a common feature in all types of apnoea of prematurity and not limited to the relatively rare obstructive apnoea attacks. Altogether 69·5% of preterm infants with apnoea have periods of airway obstruction when episodes of obstructive and mixed apnoeas are taken into account.[1] However this is clearly an underestimate if obstruction is only defined in terms of continued respiratory effort in the absence of airflow at the nose or mouth. Yet it is clear that an external obstruction will often cause preterm infants to become apnoeic even when there are no respiratory efforts against the obstruction.[2] Thus obstruction of the airway can result in a 'central' apnoea as defined by standard cardiorespiratory monitors, with absent airflow and absent respiratory efforts. Clearly an indicator of airway patency would be more useful in defining the role of airway obstruction in apnoea. One approach is to measure tidal flow using a face mask system incorporating a pneumotachograph and sensitive pressure transducer. A cardiac artefact is then transmitted on to the flow trace while the airway is patent but this is lost when the airway obstructs. Using this indirect measure of airway patency obstruction has been detected in about half of apparently central apnoeas.[3] An alternative approach is to visualise directly the upper airway during aponeic episodes and so determine its patency.

There are two likely anatomical sites for obstruction of the upper airway in apnoea, the larynx and the pharynx. Evidence exists to support obstruction at either of these sites in preterm infants with apnoea. The aim of this study was to define the site of upper airway obstruction in a group of preterm infants with severe problematical apnoea.

Patients and methods

Twelve preterm infants with severe, problematical apnoea have been studied with a median gestation of 27 weeks (range 24–31) and median birth weight 925 g (range 650–1630). The mean age at study was 30 days and a median postconceptional age of 30 weeks (range 27–36). Two infants were studied on more than one occasion. All but one had required initial ventilation for respiratory distress syndrome, mean duration 6·4 days (range 0–33). At the time of the study recurrent apnoea was a major clinical management problem and although none were oxygen dependant when studied, supplementary oxygen was often required for apnoeic episodes. Episodes of obstruction were often suspected clinically as the apnoeic episodes were sometimes associated with hypoxia and bradycardia often requiring intervention by the nursing staff.

All infants had required treatment before the study for apnoea (table 1) and all were on methylxanthine therapy. Half of the infants required further intubation and ventilation for recurrent severe apnoea after their initial period of ventilation for lung disease. Two were found to be improved when nursed with a soft support under the neck to prevent excessive neck flexion and in three infants constant stimulation was provided by ventilating an air filled mattress.

An ultrafine fibreoptic scope (PF22-Olympus) was used to visualise the upper airway of the infants studied. The scope was originally designed as an angiofibrescope for vascular surgery with an outer diameter of only 2·2 mm. A similar instrument has been used previously with success as a bronchoscope in neonates.[4] The scope has remote control two way angulation through 120° at the tip and can be directed by the operator at the hand piece.

Table 1 Treatment for apnoea

	No (%) of infants
Aminophylline/theophylline	12 (100)
Intubation and ventilation	6 (50)
Nasal continuous positive airway pressure	7 (58)
Ventilated mattress	3 (25)
Neck extension	2 (17)

Images are relayed to a colour monitor by a small endoscopic camera (OTV-S2 Olympus) connected to the scope and a continuous recording made on to VHS videotape. The fine endoscope tip is introduced intranasally and advanced and directed until located at the site of interest. In this study we have concentrated on the larynx and fig 1 shows the position of the scope relative to the surrounding structures.

Simultaneous cardiorespiratory monitoring was peformed to detect spontaneously occurring apnoeas. Respiratory efforts were detected by respiratory inductive plethysmography (Respitrace system) using only the abdominal band, as previously described, in small preterm infants.[5] Airflow at the nostril was recorded with a self retaining nasal thermistor. Oxygen saturation was also recorded (Ohmeda Biox 3700 pulse oximeter) together with heart rate. All monitor outputs were then recorded onto a four channel tape recorder (Racal Store 4DS) to provide a permanent recording of events.

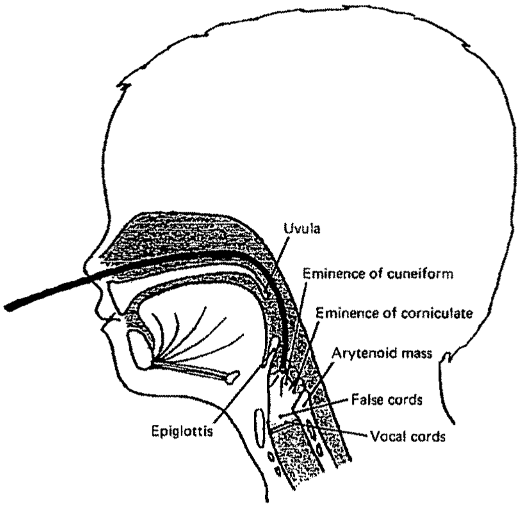


Figure 1 Position of the fibreoptic scope in relation to upper airway structures.

To enable accurate timing and recognition of apnoeic events and allow direct comparison of the endoscopic view with the monitor recordings, a further modification was made. During a study the outputs of the monitors were continuously printed out on to paper by a four channel chart recorder. This print out was then filmed by a separate free standing TV camera and relayed via a mixing box (modified Sony Video Selector ITP 265AJC) to the same colour monitor displaying the laryngoscopic view (fig 2). This meant that the monitor outputs could be directly visualised alongside the picture of the upper airway and allowed the operator to observe immediately what was happening to the airway during recorded apnoeic events. When events were subsequently analysed the split screen view with both respiratory parameters and endoscopic findings were available recorded on videotape as well as the seperate permanent recording of the respiratory monitors by the four channel tape recorder.

The procedure was well tolerated by the infants and once introduced the scope appeared

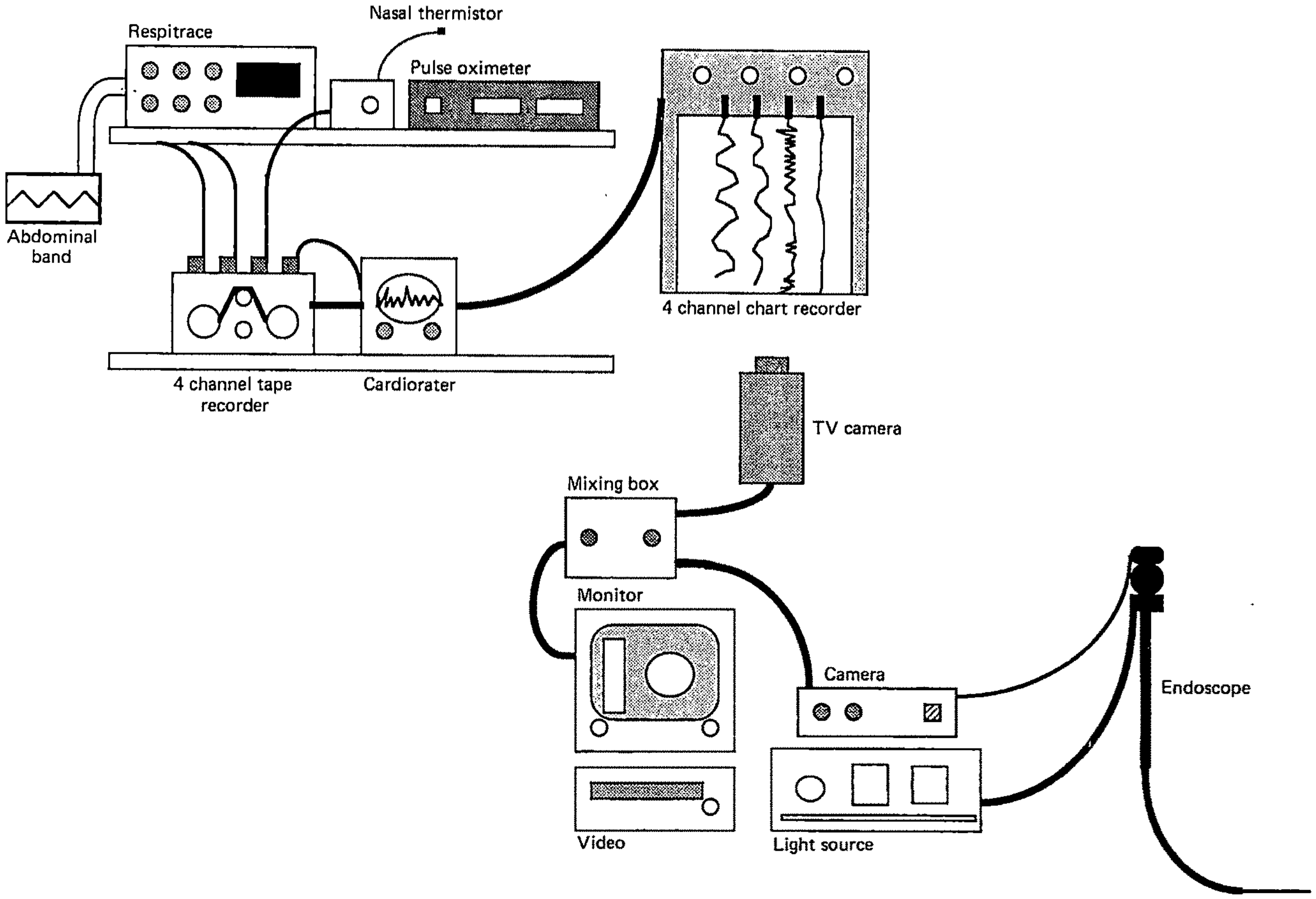


Figure 2 System to enable simultaneous visualisation of monitoring recordings and laryngoscopic view.

Table 2 Apnoeas recorded in seven infants

Patient No	*Apnoea type*	*Duration (secs)*	*Oxygen saturation drop (%)*	*Lowest heart rate (beats/min)*	*Recovery*
1	Obstructive*	19	10	150	Spontaneous
2	Mixed	50·5	36	70	Spontaneous
	Mixed	45	23	150	Spontaneous
	Mixed†	24	22	106	Intervention
3	Mixed	59	42	82	Spontaneous
4	Mixed	20	18	100	Spontaneous
	Mixed	10·7	2	171‡	Spontaneous
	Central	10·6	0	177‡	Spontaneous
	Mixed	10·5	0	170‡	Spontaneous
5	Obstructive	18	—	97	Spontaneous
	Mixed	39·2	12	90	Spontaneous
6	Central	30	32	90	Spontaneous
7	Obstructive	43	61	78	Intervention
	Obstructive	72	50	75	Intervention

*See figure 5, †see figure 6.
‡Tachycardia noted but on theophylline treatment.

to cause little discomfort or distress. Positioning of the scope was at times difficult with small movements of the baby or operator resulting in loss of the view and requiring repositioning of the scope. No increase in supplementary oxygen was necessary during the study, as judged by recorded oxygen saturations, except during apnoeic events. If the infant was on feeds these were discontinued one hour before the study and the stomach emptied to prevent aspiration.

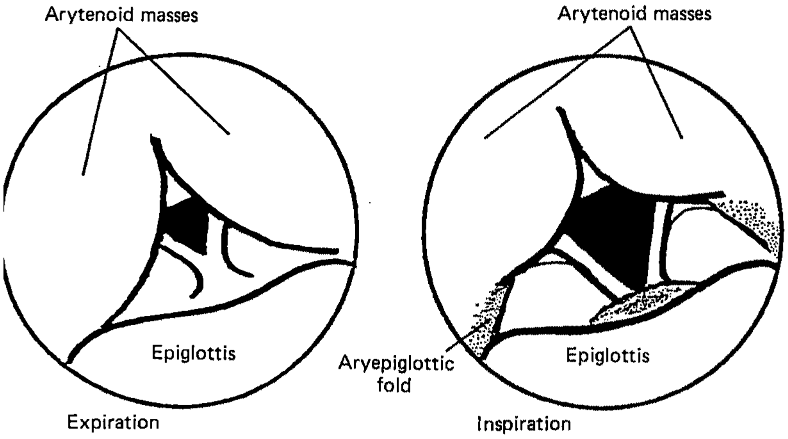


Figure 3 Laryngeal movements in tidal breathing.

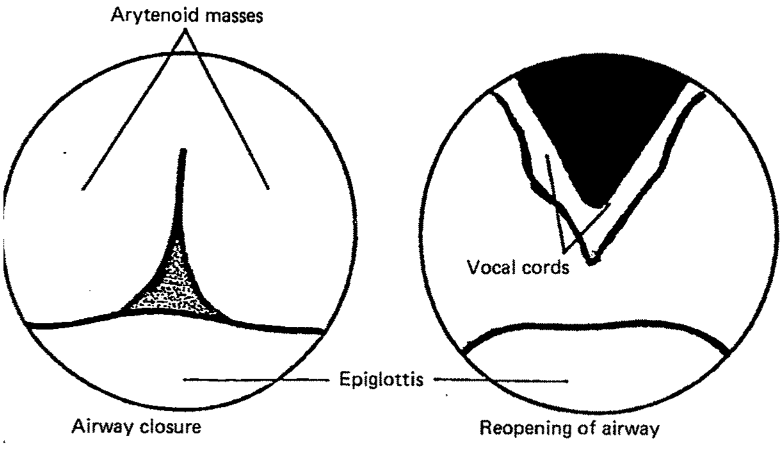


Figure 4 View of obstruction at laryngeal level during apnoea.

The infants were studied in their normal nursing position, usually prone, though some were studied supine with support to keep their neck partially extended. There were no adverse events or complications associated with the procedure.

Results

Infants were monitored for a mean time of 79 minutes (range 49–139) with simultaneous laryngoscopic visualisation for a mean time of 43 minutes (range 16–72). We were able simultaneously to record and visualise 14 apnoeic events in seven of the infants studied. The details of the apnoeas are given in table 2. Of the apnoeas recorded eight were mixed (57%), four obstructive (29%), and two central (14%) as defined by the respiratory monitors. The mean duration was 32·25 seconds (range 10·5–72). During 10 of the apnoeas a drop in oxygen saturation of 10% or greater was recorded and half had associated bradycardia of less than 100 beats/minute. No apnoeas were recorded immediately on introduction or positioning of the scope. The apnoeas recorded were not uncharacteristic of the apnoeas the infants were having before the study.

LARYNGOSCOPIC FINDINGS

The majority of recording was of normal tidal breathing with cord abduction during inspiration and narrowing of the glottic aperture in expiration (fig 3). The arytenoid cartilages with their coverings and the aryepiglottic folds are prominant structures and actively mobile in the laryngeal movements of normal tidal breathing. Swallows were frequently seen with glottic closure followed by immediate reopening of the airway.

Obstruction was observed to occur at laryngeal level during the apnoeic episodes recorded (fig 4). The prominant arytenoid masses and thick aryepiglottic folds were seen to close across the airway resulting in obstruction. This was similar to that seen during swallowing but the airway patency was not restored despite, at times, respiratory efforts against the obstruction. Figures 5 and 6 illustrate two of the apnoeic episodes recorded. The first is an obstructive apnoea with the patent laryngeal opening visualised during tidal breathing. Closure occurs at the start of the episode simultaneously with loss of airflow recorded at the nostril. Respiratory efforts continue to be made against the obstructed airway, as shown by the inductance trace, and in this example eight obstructed breaths are recorded. Airway patency is restored as airflow is again recorded with the resumption of normal respiratory effort waveforms as the obstruction is removed. The episode is associated with desaturation and a small drop in heart rate. Figure 6 is an example of a mixed apnoea with again loss of airway patency with laryngeal closure at the onset of the episode simultaneously with loss of airflow. In this case, however, there were initially no breaths against the obstruction until after about 8 seconds when respiratory efforts commence against the closed airway which remained obstructed for a further 16 seconds despite quite vigorous efforts. Again patency was restored simultaneously with the resumption of airflow. In this particular case the baby became apnoeic again shortly after and the scope withdrawn and intermittent positive pressure ventilation (IPPV) given by bag and mask. The same sequence of events was seen in the other episodes recorded including the two apparant central apnoeas with again laryngeal closure at the start of the episode with absent airflow but no respiratory efforts detected by inductance against the obstruction. Termination of the apnoea was characterised by restoration of airflow with the first respiratory effort and reopening of the laryngeal airway.

This laryngeal closure appeared to be an active process and not due to a passive collapse of the airway structures. Spontaneous recovery with reopening of the glottis and re-establishment of airway patency was seen in the majority of episodes with the scope and monitoring equipment still in position. Three episodes did require active intervention to terminate, removing the scope and providing IPPV via bag and mask, but this was not unusual for those particular infants and the apnoeic episodes. When simultaneous recording and visualisation was possible we did not record any obstructive or mixed apnoea where the larynx remained patent. In six of the apnoeas, either mixed or obstructive, the accumulation of secretions before the onset of, or the clearance of secretions with recovery from, the apnoeic episode was noticed.

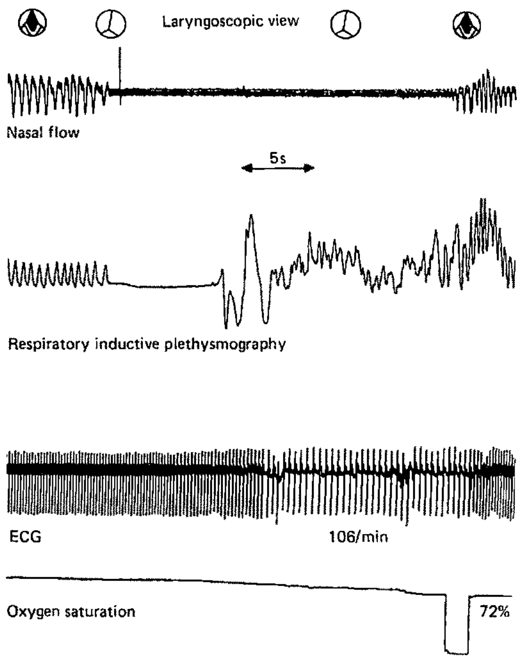


Figure 6 Mixed apnoea (patient 2). ECG, electrocardiography.

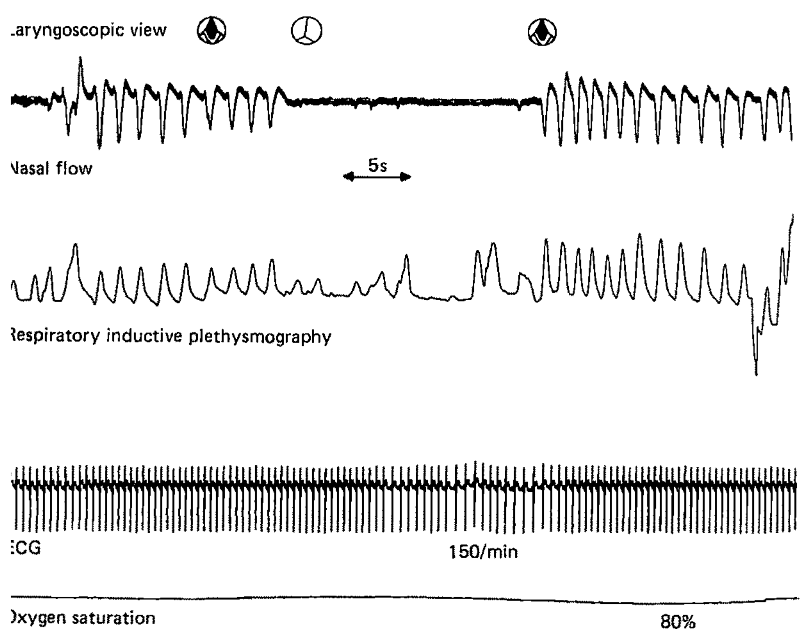


Figure 5 Obstructive apnoea (patient 1). ECG, electrocardiography.

Discussion

The suggestion that the larynx may be the site of obstruction in preterm infants with obstructive and mixed apnoea is not new. It is a common observation in apnoeic infants that on direct laryngoscopy the cords often appear tightly adducted making intubation a difficult procedure, whereas one might expect them to lie open in a hypoxic, 'flat' infant. Steinschneider and Rabuzzi also described the resumption of respiratory efforts against such a closed glottis, as would be the situation in obstructive apnoea.[6] However, it is possible that the introduction of the laryngoscope blade may itself induce glottic closure. This could also occur with our ultrafine scope yet there are a number of points to suggest that this is not the case.

Firstly, we have long periods of recording of normal tidal breathing with the scope in the same position as that during apnoeic episodes. No episodes of apnoea appeared to be precipitated by introduction or positioning of the scope. In five of the babies studied, all with recurrent apnoea, no laryngeal closure was seen for the duration of the study. We have also monitored more mature older infants with this system and have failed to see the laryngeal closure as described during these apnoeic episodes. The apnoeas recorded in our infants were typical of the episodes experienced before study and there was no apparent increase in their frequency during the study. We also recorded each 'type' of apnoea as mixed (57%), obstructive (28%), and central (14%) in the subjects and this is not far from the frequency one would expect for spontaneous apnoea particularly in a group where obstructive episodes were suspected.

In the majority of cases the apnoeas resolved spontaneously with the scope in the same position as at the onset of the episode. Research looking at laryngeal reflexes in lambs with tracheostomies showed that stimulation of various regions of the larynx with a probe, although occasionally resulting in swallows, failed to induce changes in respiratory patterns. In contrast very small volumes of hypo-osmolar fluids could produce significant respiratory depression and prolonged apnoea in the same lambs.[7] This perhaps could be studied further in premature infants by spraying local anaesthetic over the laryngeal structures before scoping but this may itself be detrimental to the baby and make observations difficult to interpret. We feel confident that when performing our studies the scope itself did not precipitate any episodes of apnoea.

There is now clear evidence of a laryngeal chemoreflex in preterm infants.[8] Stimulation of this reflex results in swallowing, airway obstruction, and apnoea. Many features of this airway protective mechanism are similar to spontaneous apnoeas and it has been suggested that an exaggeration of this reflex may be a cause of apnoea of prematurity. Preterm infants respond to fluid bolus volumes of as little as 0·01–0·1 ml introduced into the pharynx. This appears to be a chemosensitive rather than simply a mechanoreceptor response due to presence of the bolus, with the response to water being greater than saline.[9] Electrical stimulation of the superior laryngeal nerve produces glottic closure followed by prolonged apnoea in monkeys[10] with bilateral division of these nerves abolishing the swallowing and respiratory suppression induced by this reflex. Further work in adult cats has shown continuous excitation of the thyroarytenoid muscle, with visible laryngeal adduction, follows electrical stimulation of the superior laryngeal nerve. This is accompanied by cessation of respiration and also suppression of the inspiratory activity of the laryngeal abductors, the post cricoarytenoid muscles. Similar excitation of laryngeal adductors and suppression of abductors occurs with infusion of water or sodium bicarbonate.[11] Infants with malformations of the central nervous system with associated raised intracranial pressure are well documented as having apnoea and airway obstruction as a result of abductor cord paralysis.[12]

Bosma has given detailed attention to the anatomy of the newborn larynx describing it as 'a grossly mobile, enclosing composite of skeleton musculature and a more discretely mobile internal composite'.[13] The latter is composed of the arytenoid, corniculate, aciniform, and epiglottic cartilages. He also emphasises 'the disproportionate size of the arytenoid cartilages and their covering soft tissues and the prominance of the vocal, ventricular and aryepiglottic folds' resulting in a significant reduction in the size of the laryngeal lumen in comparison to that of the trachea. This agrees with our laryngoscopic findings in preterm infants with a prominant and very mobile arytenoid apparatus and the closure of these structures during airways obstruction. Swallowing produces glottic closure with cord adduction and was frequently viewed during our studies. Swallows can be produced by instillation of fluids into the oropharynx and accompany respiratory suppression as part of the laryngeal chemoreflex. The association between swallowing and apnoea has been addressed previously and has been found to occur in 76% of spontaneous prolonged apnoea.[14] It often precedes apnoea and is more frequent during mixed and obstructive apnoeas. This again illustrates the intimate relationship between apnoea and airway closure at laryngeal level.

Secretions were found to be prominant at the onset of some apnoeic episodes and often their clearance was associated with recovery and re-establishment of airway patency. Oral secretions have been shown to stimulate the laryngeal chemoreflex in animals[15] and it is possible that their accumulation in these infants may be involved in the aetiology of apnoeic episodes. It is certainly a common observation on our unit that babies with problematical apnoea often have copious, tenacious secretions and need frequent airway suction.

The other anatomical site proposed for upper airway obstruction in apnoea is the pharynx. This muscular tube like structure has a tendency to collapse when subject to negative intraluminal pressure. The pharyngeal muscles, particularly the genioglossus, serve to counteract this tendency but reduced tone in these muscles will predispose to obstruction at this level. This is particularly likely to be a problem in preterm infants or during rapid eye movement sleep. Certainly radiographic, electromyographic, and laryngoscopic studies indicate the oropharynx as the site of obstruction in adults and older infants with obstructive sleep apnoea.[16] [17] In preterm infants the use of a pharyngeal catheter monitoring pressure changes during apnoea indicated obstruction above the catheter tip high in the oropharynx in the vast majority of episodes of mixed and obstructive apnoea.[18] However, the position of the catheter tip was judged by pressure changes in normal breathing and swallowing and not confirmed by laryngoscopy or radiologically. We have not focused on regions of the pharynx in this particular study as we found evidence of obstruction at the larynx. We had no incidences when we recorded mixed or obstructive apnoea where the larynx appeared patent. It is also possible that pharyngeal airway collapse may occur secondary to laryngeal obstruction as airflow through the airway ceases.

Upper airway obstruction has been visualised during central apnoea and in periods of mixed apnoea in the absence of respiratory efforts. This correlates well with the known responses of preterm infants to an external obstruction and other indirect indicators of airway patency. Airway obstruction may therefore be a feature of all types of preterm apnoea. This suggests that the classical division into central, mixed, and obstructive apnoea may be misleading as common underlying pathophysiological mechanisms are identified.

We thank Professor D Hull for his help with the illustrations; the Foundation for the Study of Infant Death whose financial support provided the fibreoptic system; and the parents, patients, and staff at the department of neonatal medicine and surgery, Nottingham City Hospital.

1 Dransfield DA, Spitzer AR, Fox WW. Episodic airway obstruction in premature infants. *Am J Dis Child* 1983;**137**: 441–3.

2 Milner AD, Saunders RA, Hopkin IE. Apnoea induced by airflow obstruction. *Arch Dis Child* 1977;**52**:379–82.

3 Upton CJ, Milner AD, Stokes GM. Upper airway patency during apnoea of prematurity. *Annual Meeting of the British Paediatric Association.* Warwick: BPA, 1990:74.

4 Finer NN, Etches PC. Fibreoptic bronchoscopy in the neonate. *Pediatr Pulmonol* 1989;**7**:116–20.

5 Upton CJ, Milner AD, Stokes GM. Combined impedance and inductance for the detection of apnoea of prematurity. *Early Hum Dev* 1990;**24**:55–63.

6 Steinschneider A, Rabuzzi DD. Apnea and airway obstruction during feeding and sleep. *Laryngoscope* 1976;**86**: 1359–66.

7 Harned HS, Myrade J Jr, Ferreiro J. Respiratory suppression and swallowing from introduction of fluids into the laryngeal region of the lamb. *Pediatr Res* 1978;**12**:1003–9.

8 Perkett EA, Vaughan RL. Evidence for a laryngeal chemoreflex in some human preterm infants. *Acta Paediatr Scand* 1982;**71**:969–72.

9 Davies AM, Koenig JS, Thach BT. Upper airway chemoreflex responses to saline and water in preterm infants. *J Appl Physiol* 1988;**64**:1412–20.

10 Sutton P, Taylor EM, Lindeman RC. Prolonged apnoea in infant monkeys resulting from stimulation of superior laryngeal nerve. *Pediatrics* 1978;**61**:519–27.

11 Lucier GE, Daynes J, Sessle BJ. Laryngeal reflex regulation: peripheral and central neural analyses. *Exp Neurol* 1978;**62**: 200–13.

12 Holinger PC, Holinger LD, Reichert TJ, Holinger PH. Respiratory obstruction and apnea in infants with bilateral abductor vocal cord paralysis, meningomyelocele, hydrocephalus and Arnold-Chiari malformation. *J Pediatr* 1978; **92**:368–73.

13 Bosma JF. *Anatomy of the infant head.* Baltimore: Johns Hopkins University Press, 1986.

14 Menon AP, Schefft GL, Thach BT. Frequency and significance of swallowing during prolonged apnoea in infants. *Am Rev Respir Dis* 1984;**130**:969–73.

15 Harding R, Johnson P, McClelland ME. Liquid-sensitive laryngeal receptors in the developing sheep, cat and monkey. *J Physiol* 1978;**277**:409–22.

16 Guilleminault G, Hill WH, Simmons FB, Dement WC. Obstructive sleep apnoea: electromyographic and fibreoptic studies. *Exp Neurol* 1978;**62**:48–67.

17 Southall DP, Croft CB, Stebbens VA, *et al.* Detection of sleep associated dysfunctional pharyngeal obstruction in infants. *Eur J Pediatr* 1989;**148**:353–9.

18 Mathew OP, Roberts JL, Thach BT. Pharyngeal airway obstruction in preterm infants during mixed and obstructive apnea. *J Pediatr* 1982;**100**:964–8.

Archives of Disease in Childhood 1991; **66**: 793–796

Gastro-oesophageal reflux in mechanically ventilated preterm infants

L Pradeaux, V Boggio, J B Gouyon

Abstract

Long duration oesophageal pH recordings were performed on 42 mechanically ventilated and parenterally fed preterm infants for a mean (SD) of 94 (28) hours. Their mean (SD) gestational age was 31·5 (2·6) weeks and birth weight 1514 (448) g. Their mean postnatal age was 19 (10) hours at the onset of pH recording, which was performed with the babies supine. The mean hourly values for the total number of episodes of gastro-oesophageal reflux (GOR) was 2·3 (2·7), for acid GOR 1·2 (1·4), and for acid GOR longer than 5 minutes 0·08 (0·09). The time the pH was >4 (the reflux index) was 3·5 (3·3)% and the mean airway pressure was 6·6 (5·1) cm H_2O. Fifteen infants had a reflux index above 5%. GOR patterns were not significantly correlated to birth weight, gestational age, postconceptional age, ventilatory patterns, and duration of mechanical ventilation. We concluded that the reproducibility of the reflux index was low because the median of the absolute differences was 1% when two consecutive 12 hour periods were compared and reached 2·5% when the two periods were separated by 96 hours.

A second 24 hour pH recording was performed in 30 of the 42 patients after weaning from the ventilator and at a time when patients were asymptomatic and enterally fed. Compared with the late postprandial period of the second pH recording, the first recording showed an increase in the number of episodes of GOR and a decrease in reflux index, without any difference in the number of episodes of acid GOR.

Endotracheal aspiration of pharyngeal[1] or gastric contents[2] is a frequent event in mechanically ventilated newborn infants. A role for this phenomenon in the pathogenesis of bronchopulmonary dysplasia has been strongly suggested but still remains under investigation.[3] A high incidence in gastro-oesophageal reflux (GOR) has been demonstrated in ventilated adult patients[4] but limited data have failed to show similar findings in nine mechanically ventilated preterm infants.[5] Therefore, the purpose of this prospective study was to assess the patterns of prolonged oesophageal pH recordings in mechanically ventilated preterm infants.

Faculty of Medicine, University of Dijon Paediatric Service 2
L Pradeaux
J B Gouyon

Functional Research Laboratory
V Boggio

Correspondence to:
Professor J B Gouyon,
Service de Pédiatrie 2,
Hôpital d'Enfants,
Boulevard Maréchal de Lattre de Tassigny,
21034 Dijon Cedex,
France.

Accepted 26 March 1991

Patients and methods

From January 1987 to June 1989, 42 mechanically ventilated preterm infants were eligible for the study. The mean (SD) gestational age and birth weight were respectively 31·5 (2·6) weeks (range 26–36 weeks) and 1514 (448) g (range 800–2500 g).

The primary respiratory illnesses requiring intermittent positive pressure ventilation (IPPV) were delayed fetal lung fluid absorption (n=19), severe hyaline membrane disease (n=9), bacterial respiratory infection (n=2), meconium amniotic fluid aspiration (n=5), pulmonary hypertension (n=1), and hypoventilation associated with central nervous system disorders and hypotonia (n=6). Infants were ventilated either on a pressure cycled ventilator (Drager Babylog 1 and Sechrist infant ventilator IV 100B) or on a volume ventilator (Siemens Servo 900 C). Positive end expiratory pressure of 2–6 cm H_2O was used for all infants on IPPV. The ventilatory patterns may indicate the severity of the underlying pulmonary disease. Therefore, fractional inspiratory oxygen concentration, positive end expiratory pressure (PEEP), positive inspiratory pressure (PIP), and respiratory rate were recorded hourly during the whole duration of pH recordings. Mean airway pressure (MAP) was calculated according to the formula.[6]:

$$MAP=(I/E \times PIP+PEEP)/(I/E+1)$$

where I and E were respectively the inspiratory and expiratory times.

Infants were nursed in the supine position and routine care included pulmonary physiotherapy, mucus aspiration from the endotracheal tube, blood sampling, nappy changes, and setting of intravenous peripheral infusions. All these procedures were recorded because routine care is associated with significant increases in the amount of GOR.[5 7]

The oesophageal pH was recorded using a glass microelectrode (Microelectrode Inc MI 508, with a 1·2 mm outer diameter) as previously described.[8] Briefly, the pH probe was calibrated with two standard buffered solutions (pH 7·0 and 1·68). The electrode was introduced through the nose and its distal end was placed into the stomach as indicated by a fall in pH values (<4). The probe was gently withdrawn and a sudden pH increase indicated the oesophageal positioning of the probe. Thus the distal end of the probe was placed 2 to 3 cm above the lower oesophageal sphincter. The pH probe placement was confirmed by a daily chest radiograph and the probe was also calibrated each day. A skin electrocardiographic electrode was used as a reference electrode. Both electrodes were connected to a pH meter (Beckman 3500) through a patient isolation unit. The electrical signal was proportional to the pH and was fed into a strip chart recorder (Linear 1201, 4 minutes/cm, calibration: 1 pH unit/20 mm).

Taking into account the possibility of 'non-acid' reflux we computed all GOR defined as a fall in pH of more than one unit, irrespective of whether or not the pH fell below 4.[8] [9] Acid GOR corresponded to a pH fall below 4·0 during for at least 15 seconds.[7] [8] The following parameters were measured for acid GOR: the number of episodes/hour, number of episodes of GOR longer than 5 minutes/hour, and the percentage time at pH below 4 (reflux index).

A first oesophageal pH recording was started as soon as possible after the onset of mechanical ventilation. This monitoring lasted 120 hours in fasted and mechanically ventilated infants and enteral feedings or weaning from the ventilator ended the recording. No infants received sedation, muscle relaxants, or xanthine derivatives during this oesophageal pH recording. One infant died on the second day and the 41 remaining infants needed ventilatory support for 15 (15·5) days (range 2·5–58 days).

A second oesophageal pH recording was performed during 24 hours after weaning from the ventilator at a time when patients were asymptomatic, enterally fed, and did not receive any drug. Thirty of the 42 patients fulfilled these criteria.

Clinical management was constantly assumed by doctors not involved in the study.

STATISTICAL METHODS

Values were expressed as mean (SD) either for the total duration of the recordings or for each successive 12 hour period of the first recording. Additionally, 10th, 50th, and 90th centiles were calculated for GOR patterns.

The long duration of the first oesophageal pH recording allowed an assessment of the reproducibility of the results for total number of episodes of GOR and acid GOR and reflux index, the later variable being regarded as particularly informative in neonates as it is in older children and adults.[10] Each 12 hour period was compared with all the following periods for the three variables and absolute values of the differences was recorded for each infant. Because the time interval between the two periods of the comparison could influence the reproducibility of the pH recording results were expressed for intervals of 0 hour (two consecutive periods), 12, 24, 48, 36, 48, 60, 72, 84, and 96 hours. Insufficient data precluded valid calculations for time interval above 96 hours.

The data were compared using analysis of variance, the Wilcoxon test, and Fisher's exact test as needed. Pearson's test was used for correlation studies. The level of significance was 0·05.[11]

The protocol was approved by the local research ethical committee and informed consent was obtained from parents.

Results

FIRST OESOPHAGEAL PH MONITORING

Mean postnatal age at the start of the study and mean duration of the recordings were respectively 19 (10) hours (range 5–55 hours) and 94 (28) hours (range 37–120 hours).

The mean hourly values obtained for the total number of episodes of GOR was 2·3 (2·7) (range 0–129), for acid GOR 1·2 (1·4) (range 0–7), and for acid GOR longer than 5 minutes 0·08 (0·09) (range 0–0·4). The reflux index was 3·5 (3·3)% (range 0–12·1) and the mean airway pressure 6·6 (5·1) cm H_2O. Fifteen infants had a mean hourly value for reflux index above 5% (range 5·1–12·2). The distribution of underlying pulmonary diseases was not significantly different in infants with low or high reflux index: delayed fetal lung absorption 11/8, hyaline membrane disease 6/3, pulmonary bacterial infection 2/0, meconium aspiration syndrome 3/2, pulmonary hypertension 0/1, and central hypoventilation 4/2.

Table 1 summarises the data obtained for each 12 hour period of oesophageal pH recording. GOR patterns did not significantly vary during the recording. Whatever the 12 hour period GOR patterns did not significantly correlate with birth weight, gestational age, post-

Table 1 Gastro-oesophageal patterns in mechanically ventilated preterm infants. For each 12 hour period infants were included if oesophageal pH monitoring lasted at least nine hours

	Postnatal age (hours)										
	12–24 (n=17)	*24–36 (n=33)*	*36–48 (n=36)*	*48–60 (n=36)*	*60–72 (n=35)*	*72–84 (n=36)*	*84–96 (n=32)*	*96–108 (n=27)*	*108–120 (n=25)*	*120–132 (n=17)*	*132–144 (n=11)*
Mean (SD) mean airway pressure (cm H_2O)	6·8 (4·2)	7·0 (4·5)	7·4 (5·0)	7·4 (5·5)	7·5 (5·5)	6·6 (5·1)	6·3 (5·4)	5·7 (5·7)	5·4 (5·2)	5·4 (4·6)	5·7 (5·1)
10, 50, 90*	2·6, 5·8, 10·8	2·3, 6·4, 11·5	2·2, 7·5, 11·5	2·4, 7·1, 11·5	2·1, 7·3, 12·9	1·6, 6·2, 11·4	1·4, 5·9, 10·0	1·8, 4·7, 7·6	2·2, 4·0, 8·0	2·7, 4·2, 8·2	2·8, 4·4, 7·1
Mean (SD) GOR (episodes/hour)	1·5 (2·6)	3·6 (4·6)	3·0 (4·2)	2·7 (3·7)	2·2 (3·1)	1·7 (2·7)	1·8 (2·7)	1·9 (3·3)	1·3 (2·2)	1·0 (1·2)	1·5 (2·5)
10, 50, 90*	0·0, 0·6, 5·2	0·0, 2·2, 12·0	0·0, 1·6, 8·2	0·0, 1·3, 7·0	0·0, 0·9, 6·4	0·0, 1·0, 4·6	0·0, 0·7, 5·0	0·0, 0·6, 4·2	0·0, 0·5, 2·8	0·0, 0·6, 3·8	0·0, 0·5, 3·0
Mean (SD) acid GOR (episodes/hour)	0·7 (1·5)	2·0 (2·9)	1·6 (2·4)	1·3 (1·7)	1·0 (1·3)	0·8 (1·0)	1·0 (1·5)	1·0 (2·1)	0·8 (1·3)	0·6 (0·8)	0·4 (0·6)
10, 50, 90*	0·0, 0·1, 2·2	0·0, 0·7, 5·8	0·0, 0·7, 3·5	0·0, 0·2, 3·5	0·0, 0·3, 3·4	0·0, 0·4, 2·3	0·0, 0·3, 2·4	0·0, 0·2, 1·9	0·0, 0·2, 2·5	0·0, 0·2, 1·4	0·0, 0·2, 0·7
Mean (SD) acid GOR >5 minutes (episodes/hour)	0·0	0·1 (0·2)	0·1 (0·1)	0·1 (0·1)	0·1 (0·2)	0·1 (0·2)	0·1 (0·2)	0·1 (0·1)	0·1 (0·2)	0·1 (0·1)	0·1 (0·2)
10, 50, 90*	0·0, 0·0, 0·0	0·0, 0·0, 0·2	0·0, 0·0, 0·2	0·0, 0·0, 0·2	0·0, 0·0, 0·4	0·0, 0·0, 0·3	0·0, 0·0, 0·4	0·0, 0·0, 0·2	0·0, 0·0, 0·2	0·0, 0·1, 0·3	0·0, 0·0, 0·1
Mean (SD) reflux index (%) (episodes/hour)	1·2 (2·2)	4·0 (6·0)	3·8 (4·5)	3·2 (4·5)	3·7 (5·2)	3·3 (5·2)	4·3 (6·0)	3·3 (5·7)	3·3 (5·5)	3·0 (3·5)	2·5 (3·8)
10, 50, 90*	0·0, 0·0, 4·7	0·0, 0·5, 9·8	0·0, 0·4, 9·0	0·0, 0·4, 9·0	0·0, 0·3, 11·7	0·0, 1·1, 9·7	0·0, 1·1, 13·5	0·0, 0·8, 6·8	0·0, 1·2, 8·5	0·0, 1·3, 10·1	0·0, 1·7, 4·3
Mean (SD) No of care procedures	6·40 (0·84)	6·30 (0·90)	6·35 (0·83)	5·90 (0·80)	5·80 (0·80)	5·70 (0·80)	5·80 (0·75)	6·10 (1·80)	5·70 (1·10)	5·50 (0·87)	5·70 (0·80)

*Results at 10th, 50th, and 90th centiles.

Table 2 Medians of absolute differences for total number of episodes of GOR and acid GOR and reflux index between 12 hour periods of pH recording separated by 0, 12, 24, 36, 48, 60, 72, 84, and 96 hours

Time (hours) interval between the two 12 hour periods	*No of comparisons*	*GOR (episodes/ hour)*	*Acid GOR (episodes/ hour)*	*Reflux index (%)*
0	252	0·55	0·30	1
12	213	0·70	0·30	1·33
24	177	0·90	0·50	1·33
36	143	1·00	0·50	1·83
48	111	1·00	0·50	1·33
60	79	1·10	0·50	1·50
72	53	1·10	0·60	2·17
84	32	1·35	0·80	2·67
96	11	2·50	1·20	2·50

Table 3 Comparison between first pH recording and the late postprandial period of the second pH recording in 30 infants

	First pH recording	*Second pH recording*
Mean (SD) GOR (episodes/hour)	2·07 (2·26)	1·25 (0·98)*
Mean (SD) acid GOR (episodes/ hour)	1·11 (1·06)	0·92 (0·80)
Mean (SD) acid GOR >5 minutes (episodes/hour)	0·09 (0·09)	0·24 (0·33)
Mean (SD) reflux index (%)	3·70 (3·55)	7·31 (9·77)*

*p<0·05.

conceptional age, ventilatory pattern (PEEP, respiratory rate, mean airway pressure), and total duration of mechanical ventilation. The mean routine care procedures declined slightly but significantly from the first to the last 12 hour period of pH recording (table 1).

Medians for absolute differences from one 12 hour period to the following periods are indicated in table 2.

SECOND OESOPHAGEAL PH MONITORING

At the time of the second oesophageal pH monitoring the means for postnatal age, postconceptional age, and weight were respectively 38·4 (2·4) days, 6·9 (3) weeks, and 2323 (454) g. At the time of the first recording these 30 patients presented with GOR patterns similar to the whole population (table 3).

Taking into account that intragastric pH is buffered by enteral feedings in the early postprandial period (that is, the first two hours after a meal),[8] the first pH recording (without any concomitant enteral feeding) was compared with the late postprandial period of the second pH recording. The first recording presented with an increase in the total number of episodes of GOR without any difference in the number of episodes of acid GOR and a decrease in the reflux index (table 3). Reflux index values of the first recording positively correlate with values during the late postprandial period of the second pH monitoring (r=0·430, p=0·02).

Oesophageal pH recordings did not cause any side effects.

Discussion

This study clearly highlights that the first five days of life were associated with a reflux index above 5% in 36% of mechanically ventilated preterm infants when they were fasting and in the supine position. A reflux index above 5% was rarely found in two previous studies conducted in mechanically ventilated preterm infants: in three of 18 infants in the supine position[12] and one of nine infants in the prone, right lateral, and left lateral position.[5] In one study the mean for the number of episodes of acid GOR and reflux index appeared lower than in our patients: 0·51 (0·11) compared with 1·2 (1·4)/hour and 2·3 (0·6) compared with 3·5 (3·3)%.[5] We confirmed the study of Newell *et al* that the amount of reflux did not correlate with postconceptional age.[5] Nevertheless, comparisons with previous studies are of limited value because either pH recordings were of short duration[12] or infants received hourly milk feedings.[5] Milk feeding buffers intragastric pH and thus appreciably reduces acid GOR during the 120 minute postprandial period.[8, 13] By contrast, the supine position may have favoured GOR in our patients as has been previously demonstrated in mechanically ventilated preterm infants.[12]

Reproducibility of 24 hour oesophageal pH studies have been recently questioned beyond the neonatal period. Vandenplas *et al* concluded that this reproducibility was satisfactory because they found high values for Pearson correlation coefficients when comparisons were performed between pH recordings on two consecutive days in 30 infants and children.[14] Nevertheless, Hampton *et al* stressed the fact that simple correlation of pairs of results does not allow the assessment of the reproducibility of any test.[15] By analysing the differences between the pairs of results in 13 infants these authors concluded that there was a low reproducibility of pH monitoring.[15] Similarly the reproducibility of pH recording results appeared unsatisfactory for clinical applications in the mechanically ventilated preterm infants. The median of the absolute difference for reflux index was 1% when the consecutive periods were compared and reached 2·5% when the periods were separated by 96 hours. These findings did not indicate unreliability of the pH monitoring, the reproducibility of which has been demonstrated in adult patients,[16] but biological variability.

Compared with the late postprandial periods of the 24 hour pH recording performed after weaning from the ventilator, the early pH recording showed an increased number of episodes of GOR and a lower reflux index without any difference in episodes of acid GOR. This study did not allow us to state precisely the mechanism for the increased total number of episodes of GOR in the mechanically ventilated preterm infants. The prevalence of non-acid GOR during the first pH monitoring might be due to the low gastric secretion rates on the first days of birth.[17, 18]

A favourable role for IPPV on the amount of reflux has been previously suggested in preterm infants for two reasons. (1) A decline in acid GOR has been seen in mechanically ventilated infants showing respiratory distress syndrome or bronchopulmonary dysplasia compared with immediate subsequent periods of spontaneous breathing.[5, 19] (2) IPPV with end expiratory pressure was associated with a decline in the positive gastro-oesophageal pressure gradient.[5] However, we did not find any significant correlation between ventilatory pressures and GOR patterns in the first days of mechanical ventilation.

The role of endotracheal aspiration of gastric contents[2] has been strongly suggested in the pathogenesis of bronchopulmonary dysplasia.[3] This study has failed to demonstrate any significant correlation between GOR patterns in the lower third of the oesophagus and the total duration of mechanical ventilation. Recordings in the upper part of the oesophagus and in the pharynx could be better indicated in demonstrating a worsening of neonatal pulmonary diseases by GOR.

1 Goodwin SR, Graves SA, Haberkern CM. Aspiration in intubated premature infants. *Pediatrics* 1985;**75**:85–8.

2 Valat QC, Bemont F, Pegat MA, *et al.* Radionuclide study of bronchial aspiration in intensive care newborn children. *Nucl Med Commun* 1986;7:593–8.

3 Bancalari E. Bronchopulmonary dysplasia. *Pediatr Clin North Am* 1986;**33**:1–23.

4 Garo B, Geier B, Boles JM, *et al.* PHmétrie oesophagienne systématique: quelles sont la fréquence et les conséquences du reflux acide gastro-oesophagien? *Réanimation Soins Intensifs et Médecine d'Urgence* 1986;2:272.

5 Newell SJ, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Does mechanical ventilation precipitate gastro-oesophageal reflux during enteral feeding? *Arch Dis Child* 1989;**64**:1352–5.

6 Bhat R, Zikos-Labropoulou E. Resuscitation and respiratory management of infants weighing less than 1000 grams. *Clin Perinatol* 1986;**13**:285–97.

7 Newell SJ, Booth IW, Morgan MEI, Durbin GM, McNeish AS. Gastro-oesophageal reflux in preterm infants. *Arch Dis Child* 1989;**64**:780–6.

8 Gouyon JB, Boggio V, Athias P, Moreau D, Pujol HP, Spinelli A. Frequency of gastroesophageal reflux in neonates as assessed by 24-hour pH monitoring. *Helv Paediatr Acta* 1986;**41**:301–10.

9 Paton Y, MacFadyen UM, Simpson H. Sleep phase and gastro-oesophageal reflux in infants at possible risk of SIDS. *Arch Dis Child* 1989;**64**:264–9.

10 Herbst JJ. Gastroesophageal reflux. In: Lebenthal E, ed. *Textbook of gastroenterology and nutriton in infancy.* 2nd Ed. New York: Raven Press, 1989:803–13.

11 Snedecor GW, Cochran WG. *Statistical methods.* 7th Ed. Ames: Iowa State University Press, 1980.

12 Saint Martin J, Choulot JJ, Leblond C. Etude de la pHmétrie oesophagienne chez le nouveau-né de moins de 1700 grammes. *Arch Fr Pediatr* 1986;**43**:249–52.

13 Sutphen JL, Dillard RN. Effects of maturation and gastric acidity on gastroesophageal reflux in infants. *Am J Dis Child* 1986;**140**:1062–4.

14 Vandenplas Y, Helven R, Goyvaerts H, Sacre L. Reproductibility of continuous 24 hour oesophageal pH monitoring in infants and children. *Gut* 1990;**31**:374–7.

15 Hampton FJ, Mac Fadyen M, Simpson H. Reproductibility of 24 hour oesophageal studies in infants. *Arch Dis Child* 1990;**65**:1249–54.

16 Johnsson F, Joelsson BO. Reproducibility of ambulatory oesophageal pH monitoring. *Gut* 1988;**29**:886–9.

17 Euler AR, Byrne WJ, Cousins LM. Increased serum gastrin concentrations and gastric acid hyposecretion in the immediate newborn period. *Gastroenterology* 1977;**72**: 1271–3.

18 Hyman PE, Clarke DD, Everett SL, *et al.* Gastric acid secretory function in preterm infants. *J Pediatr* 1985;**106**: 467–71.

19 Sindel BD, Maisels MJ, Thomas BCh, Ballantine VN. Gastroesophageal reflux to the proximal esophagus in infants with bronchopulmonary dysplasia. *Am J Dis Child* 1989;**143**:1103–6.

Archives of Disease in Childhood 1991; **66:** 797–801

Effect of intervention on development of hip posture in very preterm babies

J A Downs, A D Edwards, D C McCormick, S C Roth, A L Stewart

Abstract

Preterm babies are physiologically hypotonic, which causes their posture to be flattened when lying in the prone position. This flattened posture may persist beyond term. In a prospective, randomised, controlled, double blind trial of postural support carried out on 45 babies born at less than 33 weeks of gestation, we showed that infants positioned with specific hip support during the period of intensive care had significantly fewer features of flattened posture at the age equivalent to term.

Extremely preterm babies, especially those who are very sick, demonstrate physiological muscle hypotonia.[1 2] When placed in the prone position they tend to lie without pelvic elevation so that the trunk and pelvis are flat on the cot, with the lower limbs abducted and externally rotated and the hips flexed to greater than 90°. Grenier observed that prolonged lying in this position resulted in a flattened posture which he termed 'frog lying'.[3] He proposed that the prolonged, excessive hip flexion resulted in shortening of the iliopsoas and adductor brevis muscles, a process that may be reversed when normal movement develops. In the neurologically abnormal infant, normal movement may not occur and the shortening may persist leading to scissoring. Grenier's hypothesis implies that some of the consequences of neurological impairment could be ameliorated by preventing the postural abnormality of the legs.

It is difficult to test this hypothesis directly because seriously neurologically impaired infants are relatively uncommon among survivors of neonatal intensive care.[4] We therefore designed a study of very preterm infants admitted consecutively to a neonatal intensive care unit to investigate whether maintaining functional postures during hospital admission prevented the development of the 'frog lying' or flattened posture.

Patients and methods

Consecutively born infants of less than 33 weeks' gestation, who were born at University College Hospital and admitted to the neonatal unit, were enrolled in the trial providing they were without genetic anomalies or congenital limb abnormalities.

Consent was obtained from the parents before entry into the study and the project was approved by the University College London faculty of clinical sciences committee on the ethics of clinical investigation.

A prospective, randomised, double blind, controlled trial was conducted. Randomisation was performed using random number tables. Preliminary calculations indicated that 20–25 subjects were needed for each group to detect a reduction in the incidence of flattened features of posture from 50% to 10% with significance at the 5% level.

PRELIMINARY STUDY

A preliminary study was conducted before the commencement of the trial in order to identify the specific features of posture of full term infants. Twenty five infants born at University College Hospital with a median gestational age of 40 weeks (range 37–42 weeks) and judged to be medically well, were examined at a median age of 4 days (range 3–14 days). These findings provided a precise definition of posture in the prone and side lying positions which were used as the normal standards to judge the success of the postural treatment in the study (see below).

TREATMENT GROUP

Specific positioning for the treatment group commenced when the infants reached 7 days of age and continued until a gestational plus postnatal age of at least 36 weeks (the age at which active muscle tone begins to develop[1]) or until discharge home.

When lying prone the babies were positioned with some pelvic elevation, the lower limbs bearing weight through the anterior knee and the hips not flexed to greater than 90° (fig 1A). In the side lying position the trunk was supported so that it was perpendicular to the cot surface with both arms comfortably forward and the bottom leg in neutral rotation (fig 1B). In the supine position both knees and elbows were supported off the cot surface to reduce hip and shoulder abduction (fig 1C). Rolled sheets or bean bags were used to support the infants. The positioning of the babies was implemented and supervised by the neonatal physiotherapist (JAD).

CONTROL GROUP

The control group was nursed according to usual nursing practice for the unit. The prone position without hip support was favoured. When in the side lying position the infants were sometimes supported with a rolled sheet or blanket but without specific attention to the line of the trunk or the position of the lower leg. No knee or elbow support was provided for the infant in the supine position.

Department of Physiotherapy, University College Hospital, London
J A Downs

Department of Paediatrics, University College and Middlesex School of Medicine, London
A D Edwards
D C McCormick
S C Roth
A L Stewart

Correspondence to:
Ms J Downs,
c/o Ms Jan Townsend,
Department of Paediatrics,
University College and
Middlesex School of Medicine,
Rayne Institute,
University Street,
London WC1E 6AU.

Accepted 5 February 1991

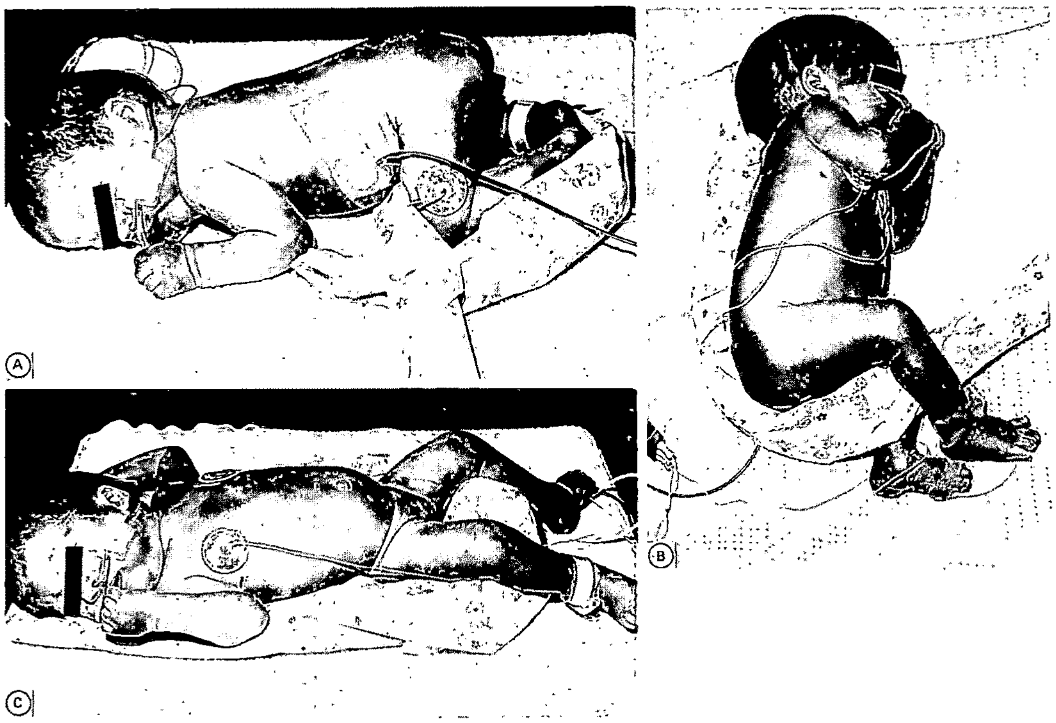


Figure 1 Postural support provided for the treatment group infants when in the (A) prone, (B) side lying, and (C) supine positions.

FOLLOW UP ASSESSMENT

Infants were assessed at a gestational plus postnatal age of 40 weeks by paediatricians during the course of neurological examination in the follow up clinic. The infants were undressed, in a quiet alert state, and medically well. The examiners, who were unaware of the group to which each baby had been assigned, performed a neurological examination[1] and a postural assessment. Each examiner had previously been trained in the assessment procedure and interobserver reliability was checked.

The postural assessment was divided into three sections:

(1) Prone lying

The baby was placed in the prone position and the weight bearing surface of the lower limb was observed. This was recorded as passing through the anterior knee, the medial knee, or the medial thigh and knee, the former category representing those babies who lay with pelvic elevation (normal) and the latter two representing those whose posture was flattened (abnormal).

(2) Side lying position

The infant was placed in a side lying position. If the infant could maintain this position independently it was recorded as stable (normal) and if not as unstable (abnormal).

(3) Supported standing

The infant was supported standing in a tray of Provil-p-base (Bayer UK Limited, Dental Products Group), a soft and non-abrasive putty, which deformed under the infant's weight to leave footprints. The line joining the tip of the first toe and the posterior aspect of the heel was defined and deviation from the position of neutral rotation was measured (fig 2).

STATISTICAL METHODS

Results in the prone and side lying positions were analysed using the χ^2 test with Yates's correction. The angles of total leg external rotation in the supported standing position were analysed using the Mann-Whitney U test.

Results

Eighty five infants were considered for the study. Three infants were ineligible for admission because of lower limb orthopaedic abnormalities and six parents did not consent to their babies being admitted to the trial. A total of 76 infants were therefore enrolled. Of these, 31 infants who had been enrolled in the study were subsequently excluded. Three study infants

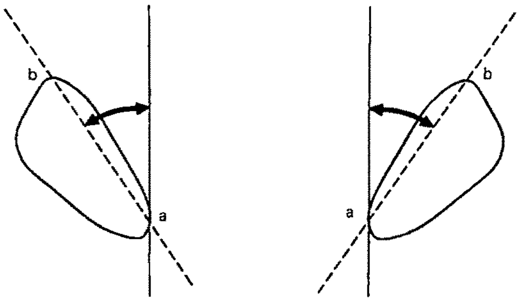


Figure 2 The point of the heel (a) and first toe (b) were marked and this was taken to represent the line of the first toe. The angles between the line of the first toe and the position of neutral rotation were measured and added to give the total number of degrees of external rotation of the legs.

Clinical details of the treatment and control groups

	Treatment group			*Control group*		
	Total (n=21)	*24–28 weeks (n=10)*	*29–33 weeks (n=11)*	*Total (n=24)*	*24–28 weeks (n=9)*	*29–33 weeks (n=15)*
Male:female	10:11	5:5	5:6	12:12	5:4	7:8
Median birth weight (g)	1332	965	1484	1252	852	1500
Range	664–2079	664–1379	965–2079	703–2180	703–1403	925–2180
Delivery:						
Vaginal	9	6	3	6	5	1
Caesarean	12	4	8*	18	4	14
Median No of days on mechanical ventilation	4	4	2	2	3	2
Range	0–26	1–26	0–10	0–25	1–25	0–8
Median No of days oxygen dependent	9	13	6	6	26	5
Range	0–182	2–182	0–73	0–108	2–108	0–34
No with abnormal neurological examination at term	12	6	6	14	8	6

*One of these infants was a breech presentation.

died (they had been allocated to the control group), three infants in the treatment group were not positioned as specified by the protocol for a period of three weeks, and 16 infants in the treatment group were transferred to another hospital or discharged home before reaching a postnatal plus gestational age of 36 weeks. Nine infants were not assessed before reaching a gestational plus postnatal age of term plus four weeks (three had been allocated to the treatment group and six to the control group) because they remained unwell in the intensive care unit or did not attend the follow up appointment. Forty five infants completed the trial, 21 in the treatment group and 24 in the control group. Clinical details are given in the table.

All 45 infants were assessed at a gestational plus postnatal age of 37–44 weeks (median 40 weeks) and the results of the posture assessment were as follows:

(1) Prone lying

Eighteen of 21 infants in the treatment group and seven of 24 in the control group lay with weight taken through the anterior surface of the knee; the remaining babies lay with weight taken through the medial knee or the medial surface of the leg. There was a significant difference between the control and treated group ($p<0.0005$). Separate analysis of the infants born at 24–28 weeks' gestation showed a significant difference between the groups ($p<0.001$) whereas there was no difference among infants born at 29–33 weeks' gestation (fig 3).

(2) Side lying position

Eighteen of 21 infants in the treatment group and nine of 24 in the control group were stable. The difference between the two groups was significant ($p<0.005$). Separate analysis of infants born at 24–28 weeks' gestation showed a significant difference between the groups ($p<0.05$) whereas there was no difference among infants born at 29–33 weeks' gestation (fig 4).

(3) Supported standing

Figure 5 shows the measured angles of external leg rotation for the treatment and control groups. The median value for the treatment group was 33° with a range of 0–120°. The median value for the control group was 40° with a range of 0–105°. The treatment group had sig-

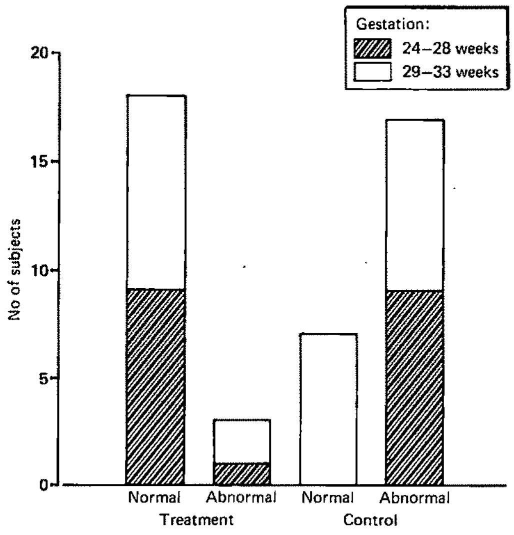


Figure 3 Histogram showing the results of the assessment of posture in the prone position for the treatment and control groups. Normal indicates those who lay with weight taken through the anterior knee and abnormal those who bore weight through the medial knee or leg.

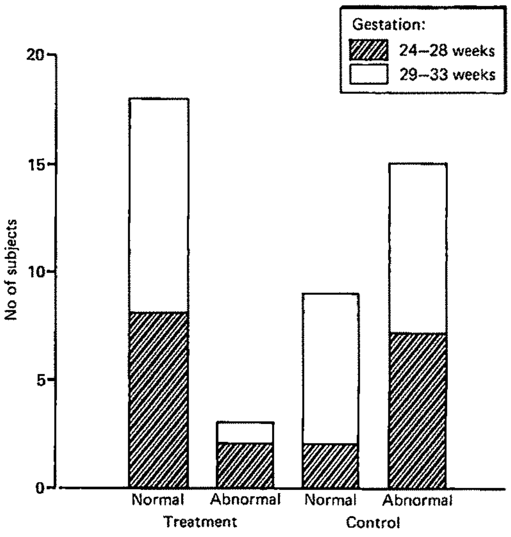


Figure 4 Histogram showing the results of the assessment of posture in the side lying position. Normal indicates those who were stable in the side lying position and abnormal those who were unstable.

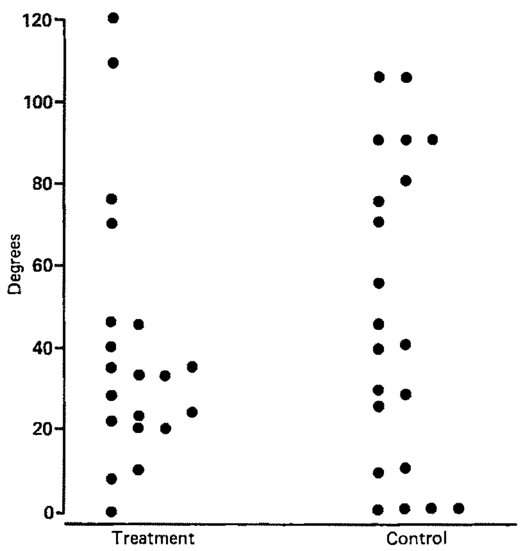


Figure 5 The angle of total leg external rotation as measured in supported standing is shown for each infant in the treatment and control groups.

nificantly smaller angles than the control group ($p<0{\cdot}01$).

Discussion

We have observed the development of flattened posture among very preterm infants, particularly those who were extremely preterm or very sick and had been nursed conventionally while undergoing neonatal intensive care. The posture was characterised by a lack of pelvic elevation in the prone lying position, excessive hip flexion, and the inability to maintain the side lying position. Other investigators have recorded similar findings. Updike *et al* described features of nursery acquired positional disorders corresponding to the flattened posture.[5] In a longitudinal study of the development of leg posture in a group of preterm babies of 25–35 weeks' gestation, Lacey *et al* found that in the prone position, 35% were weight bearing through the medial knee or leg when examined at a gestational plus postnatal age of 35–38 weeks.[6] This finding was associated with chronic oxygen dependence. By contrast, the full term lies with limbs semiflexed.[7] In the preliminary study of term infants conducted before the trial, we too noted this typical semiflexed posture. When the infants were in the prone position, there was pelvic elevation and the anterior knee bore the weight of the lower body; the full term infants were stable in the side lying position.

Grenier has drawn attention to the excessive hip flexion which is associated with the flattened posture.[3] He has suggested that this may cause shortening of the iliopsoas and adductor brevis muscle because excessive hip flexion brings the origin and insertion of these muscles closer together, and immobilised muscle adapts to the imposed length by shortening of individual sarcomeres.[8] In a child with normal neuromotor function, this deficit will be remedied with the onset of normal movement. However, a child with neurological impairment may not move adequately and will therefore be unable to overcome the muscle shortening. This could result in scissoring in the upright position, therefore affecting the stability of the hip joint and interfering with the development of walking. Grenier proposed that maintaining functional postures during neonatal intensive care would prevent this sequence of events.

Our results show that postural treatment, designed to maintain the positions noted in full term infants, can reduce flattening in very preterm infants. The postural techniques used were compatible with the infant receiving intensive care, inexpensive, simple and readily accepted by the nursing staff in the neonatal unit. The effect was significantly more noticeable in the most vulnerable infants: those born at 24–28 weeks' gestation. These infants are likely to be sick and to require mechanical ventilation and added oxygen when their muscle tone is poorly developed. It is therefore particularly gratifying that flattening was virtually abolished in the treated group. Infants born at 29–33 weeks' gestation were perhaps less likely to develop a flattened posture because of a shorter time period over which they were ill with poorly developed muscle tone. We therefore recommended that the neonatal physiotherapist's time be used to advise on and supervise the positioning of the infants in the younger gestation group.

The infants studied were typical very preterm infants undergoing intensive care in a regional referral centre. Many were very sick requiring oxygen treatment and mechanical ventilation (table). About half were judged to be neurologically abnormal at the gestational plus postnatal equivalent age of term according to standardised criteria[1] in both the treatment and control groups. On the basis of previous experience about 20% of the neurologically abnormal infants (8% of total) may be expected to present with serious neuromotor impairment causing disability by a corrected age of 12 months.[9] If Grenier's hypothesis is correct, postural support could therefore be expected to ameliorate some of the consequences of impairment in neurologically abnormal survivors of neonatal intensive care. Further follow up is in progress to assess any longer term benefits of physiological positioning for the neurologically abnormal infant. It could also be expected to help all infants by enabling them to lie comfortably on their sides. This is often the favoured position for sleep and may encourage midline orientation.[5]

The authors would like to acknowledge the advice of Professor EOR Reynolds, the support of the nursing staff in the neonatal unit and outpatient clinic at University College Hospital, Jan Townsend, coordinator of the follow up programme, and the physiotherapy department.

1 Amiel-Tison C, Grenier A. *Neurological assessment during the first year of life.* Oxford: Oxford University Press, 1986.
2 Thomas A, Saint-Anne Dargassies S. *Études neurologiques sur le nouveau-né et le jeune nourrisson.* Paris: Masson, 1952.
3 Grenier A. Prévention des déformations précoces de hanche chez les nouveau-nés à cerveau lésé. *Ann Pediatr (Paris)* 1988;35:423–7.
4 Stewart AL, Reynolds EOR, Lipscomb AP. Outcome for infants of very low birthweight: survey of world literature. *Lancet* 1981;i:1038–41.
5 Updike C, Schmidt RE, Macke C, Cahoon J, Miller M. Positional support for premature infants. *Am J Occup Ther* 1986;40:712–5.

6 Lacey JL, Henderson-Smart DJ, Edwards DA. A longitudinal study of early leg postures of preterm infants. *Dev Med Child Neurol* 1989;32:151–63.
7 Dubowitz L, Dubowitz V. *The neurological assessment of the preterm and full-term newborn infant.* London: William Heinemann Medical Publications, 1981.
8 Tabary JC, Tabary C, Tardieu C, Tardieu G, Goldspink G. Physiological and structural changes in the cat's soleus muscle due to immobilisation at different lengths by plaster casts. *J Physiol (Lond)* 1972;224:231–44.
9 Stewart AL, Hope PL, Hamilton P, *et al.* Prediction in very preterm infants of satisfactory neurodevelopmental progress at 12 months. *Dev Med Child Neurol* 1988;30: 53–63.

Commentary

POSTURAL DEFORMATION OF THE NEWBORN

Very preterm infants, and particularly those of less than 28 weeks' gestation, are very vulnerable to mechanical deformation because of the plasticity of their skeleton, the weakness and hypotonicity of their muscles, and the rapidity with which they are growing. In normal circumstances in utero they are protected from extrinsic pressures by the amniotic fluid which cushions them, makes them weightless, and permits frequent change of posture and position. After delivery they are deprived of this protection and exposed to the influence of gravity which dominates their feeble musculature and presses them statically onto the surface on which they are lying. Deformation may result especially if the infant's posture is persistent. Typically the head falls to one side and becomes flattened. With prone or supine nursing both the thorax and pelvis may also become flattened in the anterior-posterior diameter and the thighs, which usually assume the frog position, may then become externally rotated giving the lower limbs a 'Charlie Chaplin' stance.

Many of these deformities, and other less common ones, steadily diminish as the muscular-skeletal system strengthens and the infant exercises and becomes mobile. However, they *may* persist and more research is urgently required to explore and assess their long term significance. For this reason the paper on the development of hip posture by Ms Downs and her colleagues is to be welcomed, though their conclusions as to what positions and postures are 'normal' or 'abnormal' must be treated with reservation. It must be emphasised that no weight bearing posture can be considered normal for the extremely premature infant and what may be gained on the swings of one posture may be lost on the roundabouts of another. For example, when infants lie prone the authors advocate the attainment of pelvic elevation by weight bearing through the *anterior* (rather than medial) knee. To achieve this the thighs must be adducted (fig 1A). The weight of the lower body will then be transmitted to the thigh through the head of the adducted femur lying against the weak labrum and capsule of the hip joint. It remains to be seen whether or not such a posture will be associated with any increase in hip pathology. Certainly, swaddling infants with the legs in adduction and extension has a well recognised association with dislocation of the hip, and the frog position is that normally adopted for the treatment of this condition. Yet another potential hazard of adduction of the legs in the prone position is deformation of the weight bearing forefoot to produce metatarsus varus or valgus. This tiresome deformity, which was very rare in the days when British babies were all nursed supine, has now become common among prone preterm infants, unless nursed in the frog position.

In summary, this is a subject that requires further investigation, but in the meantime paediatricians and neonatal nurses should be aware of the problem and take appropriate measures to avoid deformation, including frequent changes in posture so that weight bearing forces are never allowed to persist for any length of time in one direction.

P M DUNN
Department of Child Health,
Southmead Hospital,
Southmead Road,
Bristol BS10 5NB

Archives of Disease in Childhood 1991; **66**: 802–804

Doppler assessment of pulmonary artery pressure during recovery from hyaline membrane disease

N J Evans, L N J Archer

Abstract

The changes in pulmonary artery pressure during recovery from hyaline membrane disease were studied by serial Doppler echocardiography on 37 preterm infants. Pulmonary artery pressure was assessed non-invasively by its inverse relationship with the ratio of pulmonary artery Doppler time to peak velocity and right ventricular ejection time. The pattern of rise in ratio after the acute phase of hyaline membrane disease divided into three types. In 25 infants the ratio returned to the normal range: in 12 (group 1) at the same time as the fractional inspired oxygen fell below 0·5 and in 13 (group 2) after a delay of at least 24 hours. In 12 infants (group 3) the ratio remained below the normal range during their hospital stay, suggesting pulmonary artery pressure remained high. Infants in group 3 were of significantly lower gestation and required oxygen treatment for significantly longer than infants in groups 1 and 2. Persistently raised pulmonary pressures in group 3 may reflect lung damage either directly affecting pulmonary vasculature or exerting a secondary effect on pulmonary vascular resistance through hypoxaemia.

Pulmonary hypertension is a common and serious complication of bronchopulmonary dysplasia.[1] Whether this is due to a primary effect of parenchymal lung damage sustained during mechanical ventilation or whether it is due to a secondary effect of chronic hypoxia remains unclear. High pulmonary artery pressures during the acute phase of hyaline membrane disease have been documented by both direct and indirect methods.[2 3] Whether and when pulmonary artery pressure returns to normal during the recovery period of hyaline membrane disease has not been studied.

Doppler echocardiography provides a non-invasive method to assess pulmonary artery pressure. The ratio of time to peak velocity (TPV) and right ventricular ejection time (RVET) as measured from the pulmonary artery Doppler velocity time curve has a close inverse correlation with pulmonary artery pressure. This association has been validated by comparison with direct measurements in older children and adults.[4]

We have previously reported the results of using these methods to study pulmonary artery pressure during the acute phase of hyaline membrane disease in a group of preterm infants.[3] In this paper we describe the results of using Doppler echocardiography to assess pulmonary artery pressure in the same group of infants through the recovery period until discharge from hospital.

Methods

All infants were studied using an ATL Ultramark 4 scanner with range gated pulsed Doppler. Two dimensional imaging was done with a 7·5 MHz transducer which incorporates a 5 MHz pulsed Doppler crystal.

The procedure for each study was as follows. The pulmonary artery was visualised from the parasternal long axis view. The Doppler sample volume was placed just distal to the pulmonary valve and the Doppler pattern was recorded and frozen on screen. The time intervals were measured using the incorporated Doppler measurement calipers, a print was then taken. TPV was measured as the time interval between the systolic Doppler waveform leaving the baseline and reaching its peak velocity. RVET was the time interval between the systolic waveform leaving and returning to the baseline. A mean of three systoles was taken. A second 'blind' observer repeated the measurements on 50 of the Doppler prints using a computer digitiser system. The correlation coefficient between the 'on line' and 'blind' measurements was 0·92. The ductus arteriosus was then visualised from the high left parasternal view. The Doppler sample volume was placed in the pulmonary end of the duct and the flow pattern recorded. The duct was assessed as closed when it could not be visualised and no flow could be detected on a pulsed Doppler search of the pulmonary end of the duct.

Thirty seven preterm infants were studied. Mean gestation was 30·5 weeks (range 26–37 weeks) and mean birth weight 1570 g (range 720–2960 g). All infants had hyaline membrane disease, the parameters of disease severity are shown in table 1. No infant received muscle relaxants or inotropic support during the phase of the illness described in this paper. For the purposes of this study the acute phase of hyaline membrane disease was defined as the period until the fractional inspired oxygen (FIO_2) had peaked and returned to below 0·5; these results have been previously reported.[3] The recovery phase described in this paper was the subsequent period until discharge from hospital. Infants were studied initially every 24 hours, this interval increased, as recovery continued, to approximately twice weekly. At the time of each study a record was kept of oxygen requirements, ventilator settings, and most recent blood gases. Infants were studied until either

**Neonatal Unit,
John Radcliffe
Maternity Hospital,
Oxford**
N J Evans
L N J Archer

Correspondence to:
Dr N J Evans,
Department of Paediatrics,
John Radcliffe Hospital,
Headington,
Oxford OX3 9DU.

Accepted 13 December 1990

Table 1 Parameters of disease severity in the 37 infants

Ventilated (n=35)	
Maximum FIO$_2$:	
<0·6 (n=5)	
0·6–0·9 (n=16)	
>0·9 (n=16)	
Mean (range) maximum FIO$_2$ 0·79 (0·35–1·0)	
Mean (range) maximum mean airway pressure during acute phase	12·8 cm H_2O (5·5–25·5)
Mean (range) length acute phase	85 hours (12–234)
Median (range) ventilation time	184 hours (58–5880)

they were spontaneously breathing air and the TPV:RVET ratio was within the normal range or until they were discharged from hospital. The normal range for TPV:RVET was derived from the postnatal steady state ratio achieved in a group of 19 healthy preterm infants (0·34 to 0·41).[5]

Statistical analysis was by Student's *t*, Mann-Whitney, and Wilcoxen tests, and linear regression analysis. Significance was accepted at p values of <0·05. The study was approved by the Central Oxford research ethics committee.

Results

In all infants TPV:RVET ratio rose in the early recovery period above the levels seen during the acute phase. The pattern of change in TPV:RVET fell into three groups. In 12 infants, group 1, the ratio rose rapidly into the normal range within 24 hours of the oxygen requirements falling (fig 1). In 13 infants, group 2, there was a delay of more than 24 hours between the FIO$_2$ falling to below 0·5 and the ratio rising into the normal range (fig 2). The median delay was 103 hours with a range from 24 to 286 hours. And in 12 infants, group 3, the TPV:RVET did not rise into the normal range during the time of study (fig 3). The length of follow up of the infants in group 3 ranged from 336 to 5880 hours (14 to 245 days) with a median of 1380 hours (58 days). The TPV:RVET ratio taken just before discharge, or in one case death, ranged from 0·19 to 0·33 with a mean of 0·26. Eleven of these infants were breathing air at the time of discharge. One infant developed severe bronchopulmonary dysplasia requiring continuing ventilation in an FIO$_2$ of 0·5; this infant's TPV:RVET was between 0·19 and 0·24 for most of the recovery period. He died in right heart failure at 35 weeks of age. Six of the 12 infants in this group showed a similar pattern of change in TPV:RVET as is shown in fig 3. In the early recovery period the ratio rose towards the normal range but fell as the recovery period continued. In the other six infants, which included the infant with severe bronchopulmonary dyplasia, the ratio remained at a relatively consistent low level throughout the recovery period.

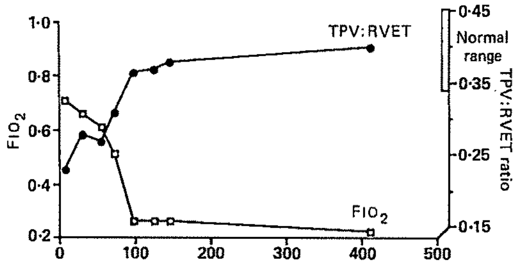


Figure 1 FIO$_2$ and TPV:RVET ratio plotted against postnatal age in an infant of 27 weeks' gestation. This was typical of infants in group 1, where the ratio rose at the same time as FIO$_2$ fell.

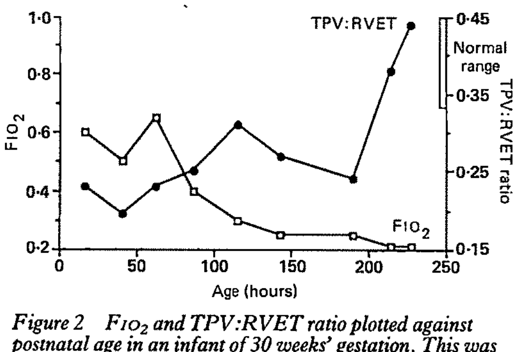


Figure 2 FIO$_2$ and TPV:RVET ratio plotted against postnatal age in an infant of 30 weeks' gestation. This was typical of the infants in group 2, where there was a delay in the rise of the ratio.

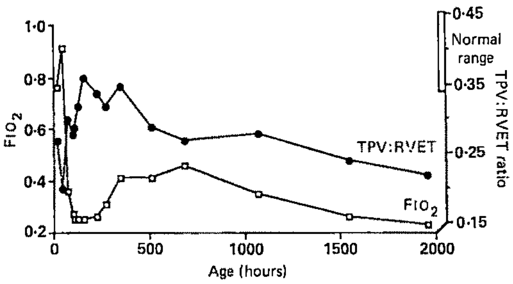


Figure 3 FIO$_2$ and TPV:RVET ratio plotted against postnatal age in an infant of 28 weeks' gestation. This was typical of the infants in group 3, where the ratio did not rise into the normal range.

There were slight differences in the mean heart rate at the time of study. Mean (SD) heart rate for the healthy infants was 144 (15). The mean heart rates in groups 2 and 3, respectively 155 (14) and 157 (17), were higher than that in group 1 (135 (18)). Apart from between groups 2 and 3, the differences in mean heart rate between the groups were significant, p<0·01. There was no correlation between TPV:RVET and heart rate, either overall or within each group.

Table 2 compares variables of respiratory disease severity and maturity between the three groups. The median gestation was progressively significantly lower between the groups 1 through to 3. Group 1 had significantly higher median birth weight than group 3. Each infant's mean acute phase ratio was significantly lower in group 2 than group 1 but was not significantly lower in group 3. The differences in time to duct closure were not significant, but groups 2 and 3 were ventilated for significantly longer than group 1. The infants in group 3 required oxygen treatment for significantly longer than groups 1 and 2 with all but two of them requiring extra inspired oxygen for more than 28 days (672 hours).

Table 2 Maturity and clinical course in the three groups

	Group 1 (n=12)	*Group 2 (n=13)*	*Group 3 (n=12)*	*Significance (p value)*
Median (range) gestation (weeks)	34 (27–37)*	30 (28–34)*	28 (26–34)*	<0·05
Median (range) birth weight (g)	2400 (900–2960)*	1200 (900–2300)	1050 (720–2350)*	<0·05
Mean (SD) acute TPV:RVET	0·27 (0·026)*	0·23 (0·032)*	0·25 (0·037)	<0·01
Mean (range) time duct closure noted (hours)	108 (24–264)	152 (12–336)	151 (13–984)	NS
Median (range) duration ventilation (hours)	116 (0–408)* **	285 (74–1224)**	844 (98–5880)*	<0·01
Median (range) time in oxygen (hours)	189 (112–408)**	170 (76–1224)*	1128 (260–5880)* **	<0·001

*For each parameter there are three statistical pairings: when all are significantly different, each group has an asterisk; when two pairs are different, one pair has one and the other two asterisks.

Discussion

The two factors other than pulmonary artery pressure which will affect the TPV of pulmonary artery flow are heart rate and myocardial contractility. As the heart rate increases the TPV will be reduced.[6] This effect is reduced, but not eliminated, by expressing the TPV as a ratio to RVET.[6] We could find no association between heart rate and TPV:RVET within this study though there were small but significant differences between the mean heart rates of the groups of infants with hyaline membrane disease and the healthy infants. From the data of Serwer *et al*,[6] we would expect the differences in mean heart rate between the groups to reflect in a change in TPV:RVET of about 0·01. It is unlikely that this would affect the results described in this paper. Reduced myocardial contractility will prolong the TPV. Right ventricular function was not formally assessed in this study. However only the infant who died was considered to have reduced right ventricular contractility on imaging.

Eleven of the 37 infants in this study still had Doppler evidence of high pulmonary artery pressure at the time of their discharge from hospital. Despite this, at discharge these infants were breathing spontaneously in air. The prolonged need for oxygen treatment and the lower gestation of this group would suggest that these were the infants who had sustained a degree of damage to their lungs during the acute phase of their illness. Respiratory problems are common after discharge from neonatal intensive care and abnormalities of respiratory function can be detected up to 7 years of age.[7] It seems likely that there is a range of damage sustained by the lungs during ventilatory support for hyaline membrane disease, with only the more severe form manifesting as a continuing recognised requirement for ventilation and oxygen treatment. Pulmonary hypertension has been well documented as a complication of these severe forms of bronchopulmonary dysplasia.[1] One infant in the group that we studied developed severe bronchopulmonary dysplasia; that infant had a persistently very low TPV:RVET and died at 35 weeks of age in right ventricular failure. Our data would suggest that there is also a range of raised pulmonary vascular resistance; and that even milder degrees of lung damage, which do not require long term oxygen treatment, have continuing evidence of raised pulmonary artery pressure.

In bronchopulmonary dysplasia some of the raised pulmonary vascular resistance probably results directly from parenchymal lung damage but there is evidence that it may in part be a secondary effect of hypoxia.[1] Hypoxia is a potent pulmonary vasoconstrictor and, if chronic, may lead to alteration in the structure of the pulmonary vascular bed. Such changes have been seen at necropsy in cases of bronchopulmonary dysplasia.[8] In addition, catheter studies in infants with severe bronchopulmonary dysplasia have shown that in many cases pulmonary artery pressure will fall if 100% oxygen is inspired.[1] In half the infants in group 3 of our study, the TPV:RVET fell as the recovery period continued. It seems possible that borderline low levels of oxygen or unrecognised hypoxaemic periods may be sustaining high pulmonary artery pressure in those infants. Pulse oximetry provides a good non-invasive means to monitor oxygenation in those infants.[9] It may be that continuous monitoring of infants who have had a prolonged need for oxygen treatment should become routine, even after transfer into air. The presence of a low TPV:RVET ratio may provide a further pointer to those infants in whom particularly close attention to oxygenation is needed. Further study is required to clarify those points.

Further study is also needed to follow up a group of these infants beyond their discharge from hospital. Firstly, to establish whether and when the ratio returns to the normal range and secondly, to see if a low ratio is associated with a higher risk of postneonatal respiratory problems.

We thank Dr Andrew Wilkinson and Dr Peter Hope for their help and encouragement and for allowing us to study infants under their care. We also thank Sheila Hayes for typing the manuscript.

1 Goodman G, Perkins RM, Anas NG, *et al.* Pulmonary hypertension in infants with bronchopulmonary dysplasia. *J Pediatr* 1988;112:67–72.

2 Moss AJ, Emmanouilides GC, Petteri O, Higashino SM, Adams FH. Postnatal circulatory and metabolic adjustments in normal and distressed premature infants. *Biol Neonate* 1965;8:177–97.

3 Evans NJ, Archer LNJ. Doppler assessment of pulmonary artery pressure and extra-pulmonary shunting in the acute phase of hyaline membrane disease. *Arch Dis Child* 1991; 66:6–11.

4 Kitabatake A, Inoue M, Asao M, *et al.* Non-invasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;68:302–9.

5 Evans NJ, Archer LNJ. Postnatal circulatory adaptation in healthy term and preterm newborns. *Arch Dis Child* 1990; 65:24–6.

6 Serwer GA, Cougle AG, Eckerd JM, Armstrong BE. Factors affecting use of the Doppler-determined time from flow onset to maximal pulmonary artery velocity for measurement of pulmonary artery pressure in children. *Am J Cardiol* 1986;58:352–6.

7 Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Silverman M. Lung function in children of low birthweight. *Arch Dis Child* 1989;64:1284–93.

8 Tomashefski JF, Oppermann HC, Vawter GF, Reid LM. Bronchopulmonary dysplasia: a morphometric study with emphasis on the pulmonary vasculature. *Pediatr Pathol* 1984;2:469–87.

9 Southall DP, Bignall S, Stebbens VA, *et al.* Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987;62: 882–8.

rchives of Disease in Childhood 1991; 66: 805–807

Absent or reversed end diastolic flow velocity in the umbilical artery and necrotising enterocolitis

G Malcolm, D Ellwood, K Devonald, R Beilby, D Henderson-Smart

Abstract

Absent or reversed end diastolic flow (AREDF) velocities in the umbilical artery were identified in 25 high risk pregnancies. In six pregnancies the fetus was abnormal and all but one of these ended in perinatal death. Of the 19 morphologically normal fetuses, three died in utero and there were four neonatal or infant deaths. The mortality rate was 48% for all pregnancies and 37% for those with morphologically normal fetuses. There was a highly significant increased risk for the development of necrotising enterocolitis in those morphologically normal fetuses with AREDF (53%) compared with controls (6%) who did have umbilical artery end diastolic flow velocities in fetal life. There were no significant differences between the matched pairs for parameters of neonatal outcome chosen to reflect neonatal morbidity. These findings demonstrate the close association between AREDF and necrotising enterocolitis that appears to be independent of other variables such as degree of growth retardation, prematurity, and perinatal asphyxia.

Doppler ultrasound technology has made it possible to study the flow characteristics of the fetal circulation.[1] Over the past decade many data have been reported which link abnormal umbilical artery flow velocity waveforms with growth retardation and perinatal asphyxia.[2 3] However, the exact role for such measurements in the management of high risk pregnancy remains unclear.[4] Recent reports have suggested an association between very abnormal umbilical artery and fetal aorta Doppler studies showing absent or reversed end diastolic flow (AREDF) velocities and severe neonatal morbidity including necrotising enterocolitis.[5 6] This may simply reflect the fact that very growth retarded, preterm fetuses are more likely to demonstrate AREDF and will often develop necrotising enterocolitis. This paired analysis study was designed to test the hypothesis that it is AREDF, independent of growth retardation and prematurity, which predisposes to necrotising enterocolitis.

King George V Hospital for Mothers and Babies, Camperdown, NSW, Australia,
Department of Perinatal Medicine
G Malcolm
Department of Fetal Medicine
D Ellwood
K Devonald
R Beilby
D Henderson-Smart

Correspondence to:
Associate Professor D Ellwood,
University of Sydney,
Department of Obstetrics and Gynaecology,
Nepean Hospital,
Penrith, NSW 2750,
Australia.

Accepted 28 February 1991

Methods

Over a three year period (April 1987 to April 1990) over 1000 high risk pregnancies were monitored by the recording of flow velocity waveforms from the umbilical artery. All fetuses were studied using a GE RT3600 ultrasound system with pulsed Doppler. Waveforms were obtained using a 5 MHz phased array sector transducer, and a 100 Hz wall filter was used. In each study waveforms were continuously displayed until an optimum signal was obtained and then five consecutive waveforms selected for analysis. Waveforms were analysed for both maximum systolic:minimum diastolic ratio (A:B ratio) and pulsatility index.[7] The results of Doppler studies were not revealed to obstetricians or neonatologists involved in the management of these pregnancies. The study was approved by the hospital ethics committee and all patients gave informed consent.

From these pregnancies 25 cases were identified in which there was AREDF in the umbilical artery. Liveborn fetuses without congenital malformations were subjected to analysis of parameters of neonatal outcome. One neonate who survived two hours only was excluded from further analysis. These neonates were matched for gestational age and birth weight with neonates in whom Doppler studies had consistently shown end diastolic flow in the umbilical artery before delivery. Controls were drawn from the nursery population during the same time period as the cases and were chosen for best fit for both birth weight and gestational age.

For the matched pairs the following were analysed as dichotomous variables:

(1) Respiratory distress defined as over six hours supplemental oxygen or respiratory support.

(2) Perinatal asphyxia defined as any one of these criteria: cord arterial pH <7·15, base deficit >9 mmol/l, Apgar score <4 at one minute or 7 at five minutes.

(3) Neutropenia ($<2\times10^9$/l neutrophils) and/or thrombocytopenia ($<100\times10^9$/l platelets) on initial blood count.

Necrotising enterocolitis was classified as none, suspect, or proved. The suspect group had the clinical features of necrotising enterocolitis (that is, abdominal distension, bile aspirates or vomiting, blood in the stools, and systemic illness) and were treated with parenteral nutrition and antibiotics. Proved cases had in addition the radiological features of pneumatosis coli, perforation, or gas in the portal circulation. Laparotomy or necropsy evidence was also classified as proved necrotising enterocolitis.

Neonatal radiographs and ultrasound scans were reviewed by a paediatric radiologist without knowledge of the clinical history. All the neonates less than 32 weeks' gestation, all ventilated neonates, and all those with abnormal neurological signs received routine cranial ultrasound examinations in this nursery. The number of days of positive pressure ventilation and maximum supplemental oxygen concentration were analysed as continuous, non-parametric variables. Birth weights, all being below the 20th centile, were treated as continuous, non-parametric variables. Birth weight and head circumference at birth were standardised to the normal population before analysis.[8] Statistical methods used were the Wilcoxon rank sum test for continuous variables, McNemar's test for paired dichotomous outcome variables, and Fisher's exact test for unpaired dichotomous outcome variables. For the necrotising enterocolitis data proved and suspected cases were combined and the data analysed as matched pairs by McNemar's test.

Results

During this period 25 pregnancies were identified in which fetuses showed AREDF. The pregnancies were complicated by hypertension (n=11), obstetric lupus syndrome (n=3), unexplained growth retardation (n=3), renal failure (n=1), twins (n=1), and congenital malformations (n=6). Those with congenital malformations have been excluded from further analysis. Of the 19 morphologically normal fetuses three died in utero and one died within 24 hours of birth, leaving 15 neonates (the cases) to be matched with controls. The overall mortality in fetuses with AREDF was 48% (12/25). Excluding congenital malformations the mortality was 37% (7/19). The three neonates from the case group of 15 who died did so at 42, 180, and 190 days respectively. The causes of death were complications of fulminating necrotising enterocolitis in the first of these and chronic lung disease in the second and third. There were no deaths in the control group.

MATCHED PAIRS

The gestational age at delivery ranged from 26–35 weeks (mean (SD) 30·5 (2·95) weeks) for the cases and 26–34 weeks (mean (SD) 30·4 (2·85) weeks) for the control group. The birth weight ranged from 504–1635 g (mean (SD) 1059 (343) g) in the cases and 515–1748 g (mean (SD) 1079 (353) g in the control group. There were no significant differences between the cases and controls for birth weight (p=0·85) or gestational age (p=0·82) by Wilcoxon rank sum test. There were eight boys and seven girls in the cases and four boys and 11 girls in the control group.

The characteristics of the matched pairs are shown in table 1. Table 2 shows the incidence of proved or suspect necrotising enterocolitis in the two groups. There is a highly significant increase in the incidence of necrotising enterocolitis in neonates who demonstrated AREDF ($\chi^2=5\cdot14$, df 1, $0\cdot05>p>0\cdot01$ by McNemar's test).

When matched pairs were examined for the presence of asphyxia there were five discordant pairs but in four of these the direction was towards the control. Similarly for respiratory distress there were six discordant pairs with the direction being towards the control in five.

Table 2 Incidence of necrotising enterocolitis

	Proved	*Suspect*	*None*
Cases	5	3	7
Controls	1	0	14

Table 3 Morbidity assessed by days of positive pressure ventilation and maximum supplemental oxygen

	Day of ventilation		*Maximum oxygen concentration (%)*	
	Mean (SD)	*Range*	*Mean (SD)*	*Range*
Cases	14 (30)	0–100	41 (24)	21–100
Controls	9 (13)	0–40	54 (32)	21–100

There were no significant differences between the matched pairs for days of ventilation (p=0·62) and maximum oxygen concentration (p=0·27) by the Wilcoxon rank sum test.

Table 1 Details of case-control pairs

Pair		*Sex*	*Birth weight (g)*	*Gestational age (weeks)*	*Head circumference (cm)*	*Asphyxia*	*Respiratory distress*	*Necrotising enterocolitis*	*Neutropenial thrombocytopenia*
1	Case	F	670	28	23·8	Yes	No	Suspected	Yes
	Control	F	680	28	23·5	Yes	Yes	None	Yes
2	Case	F	1635	35	30·2	No	No	Proved	Yes
	Control	F	1748	34	30·5	No	No	None	No
3	Case	M	800	28	25·0	No	Yes	Proved	Yes
	Control	F	846	28	25·0	Yes	Yes	None	Yes
4	Case	M	1305	34	28·0	No	No	None	Yes
	Control	F	1235	33	28·5	No	No	None	No
5	Case	F	1400	33	28·5	No	No	None	Yes
	Control	F	1540	33	28·7	No	Yes	None	No
6	Case	M	920	28	25·0	No	Yes	None	No
	Control	F	860	28	25·0	No	Yes	None	No
7	Case	F	540	27	20·9	No	Yes	Suspected	Yes
	Control	M	515	27	22·5	Yes	Yes	None	Yes
8	Case	M	967	31	27·4	No	No	Suspected	No
	Control	F	1055	32	26·0	No	No	Proved	No
9	Case	M	1100	30	27·5	No	No	None	Yes
	Control	M	1175	30	27·7	Yes	Yes	None	Yes
10	Case	M	623	26	23·0	Yes	Yes	None	No
	Control	F	654	26	25·0	Yes	Yes	None	No
11	Case	M	1047	29	27·1	No	No	Proved	No
	Control	F	1114	29	26·1	Yes	Yes	None	No
12	Case	F	875	29	25·5	Yes	No	Proved	Yes
	Control	M	910	28	25·0	Yes	Yes	None	Yes
13	Case	F	1500	34	29·5	No	No	None	Yes
	Control	M	1375	34	31·2	No	No	None	No
14	Case	M	1470	34	31·0	No	No	None	No
	Control	F	1480	34	28·5	No	No	None	No
15	Case	F	1069	32	26·1	Yes	Yes	Proved	Yes
	Control	F	995	32	27·5	No	No	None	No

However, for haematological abnormalities the five discordant pairs were all in the direction of the cases. This just fails to reach significance at p=0·07 (McNemar's test). There were no significant differences between the matched pairs for neonatal morbidity assessed by days of positive pressure ventilation or maximum supplemental oxygen concentration (table 3). There were two cases of periventricular haemorrhage (one grade 3 and one grade 4), both in the index group.

Discussion

These data clearly demonstrate the poor outcome in pregnancies in which umbilical artery blood flow shows AREDF, with a corrected mortality rate of 37% in this series. This figure is the same as that arrived at by Pearce in a meta-analysis of a number of studies of similar pregnancies.[6] Moreover, the poor neonatal outcome suspected from these uncontrolled series is confirmed by a paired analysis which shows the highly significant increased risk for liveborn fetuses of developing necrotising enterocolitis. By analysing other parameters of neonatal outcome that may predipose to necrotising enterocolitis, such as standardised birth weight, gestational age, asphyxia, and need for ventilator support it appears that this increased risk of necrotising enterocolitis may be independent of these other variables. Larger numbers of patients may have revealed a significant association between necrotising enterocolitis and haematological abnormalities such as neutropenia and thrombocytopenia.

The conclusion can be drawn that it is not just the smallest and sickest neonates who show AREDF and then go on to develop necrotising enterocolitis. Therefore, it may be inferred that the presence of AREDF must have some significance for the aetiology of necrotising enterocolitis. Although there is no unifying concept of the aetiology of necrotising enterocolitis, underperfusion and/or hypoxia of the gut are thought to be among the more important aetiological factors.[9] An association between fetal compromise and redistribution of fetal blood flow has been demonstrated by analysis of internal carotid and umbilical artery Doppler studies.[10] It has been proposed that blood flow redistribution to the head, myocardium, and adrenals may explain the 'brain sparing' effect seen in some growth retarded neonates.[11] This redistribution may predispose the neonate to necrotising enterocolitis by sacrificing flow in the descending aorta and consequently in the splanchnic circulation. The mechanism of 'head sparing' may therefore predispose the fetus to necrotising enterocolitis. Analysis of the ratio of standardised head circumference to standardised birth weight does not, however, show a difference either between the two groups or within the index group between those with and without necrotising enterocolitis. This may be explained by the early onset of growth retardation in many of these cases. Further study of blood flow redistribution using Doppler is warranted. The demonstration of AREDF places the fetus at high risk of perinatal or infant death. The neonate is also at considerable risk of developing necrotising enterocolitis. Neonatologists should be alerted to this finding to facilitate preventative treatment or early detection of necrotising enterocolitis.

AREDF could also be used in case finding for prospective, controlled trials of necrotising enterocolitis prevention or treatment. Obstetricians should also be aware of the high incidence of fetal abnormality in the growth retarded fetus with AREDF.

We would like to thank Dr J Anderson and Dr A Boogert for allowing us to study their patients. We also thank Ms Deborah Edwards for statistical advice.

1 FitzGerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: a new method. *BMJ* 1977;**ii**:1450–1.
2 Trudinger BJ, Cook CM, Jones L, Giles WB. A comparison of fetal heart-rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. *Br J Obstet Gynaecol* 1986;**93**:171–5.
3 Fleischer A, Schulman H, Farmakides G, Bracero L, Blattner P, Randolph G. Umbilical artery velocity waveforms and intrauterine growth retardation. *Am J Obstet Gynecol* 1985;**151**:502–5.
4 Trudinger BJ, Cook CM, Giles WB, Connelly A, Thompson RS. Umbilical artery flow velocity waveforms in high-risk pregnancy. Randomised controlled trial. *Lancet* 1987;**i**: 188–90.
5 Hackett GA, Campbell S, Gamsu H, Cohen-Overbeek T, Pearce JMF. Doppler studies in the growth retarded fetus and prediction of neonatal necrotising enterocolitis, haemorrhage and neonatal morbidity. *BMJ* 1987;**294**:13–6.
6 Pearce JM. Doppler ultrasound blood velocity waveforms. In: Spencer JAD, ed. *Fetal monitoring; physiology and techniques of antenatal and intrapartum assessment.* Tunbridge Wells: Castle House, 1989:78–84.
7 Gosling RG, King DH. Ultrasonic angiology. In: Hascus AW, Adamson L, eds. *Arteries and veins.* Edinburgh: Churchill Livingstone, 1975:61–98.
8 Kitchen WH, Robinson HP, Dickson AJ. Revised intrauterine growth curves for an Australian hospital population. *Aust Paediatr J* 1983;**19**:157–61.
9 Pearse RG, Roberton NRC. In: Roberton NRC, ed. *Textbook of neonatalogy.* Edinburgh: Churchill Livingstone, 1986: 752–5.
10 Wladimiroff JW, Noordam MJ, Van den Wijngaard JAGW, Hop WCJ. Fetal internal carotid and umbilical artery waveforms as a measure of fetal well-being in intrauterine growth retardation. *Pediatr Res* 1988;**24**:609–12.
11 Campbell S, Thoms A. Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol* 1977;**84**:165–74.

Fibrinolysis in cerebrospinal fluid after intraventricular haemorrhage

A Whitelaw, L Creighton, P Gaffney

Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London and Department of Paediatrics, Aker University Hospital, 0514 Oslo 5, Norway
A Whitelaw
Haematology Department, National Institute for Biological Standards and Control, South Mimms, Hertfordshire
L Creighton
P Gaffney
Correspondence to: Dr Whitelaw.

Accepted 28 February 1991
(Arch Dis Child 1991;66:808–809)

Abstract
Concentrations of cross linked fibrin degradation products were measured in the cerebrospinal fluid from five 'normal' preterm infants (median 102 ng/ml), four preterm infants with intraventricular haemorrhage (median 315 ng/ml), and five infants with progressive posthaemorrhagic ventricular dilatation (median 1000 ng/ml). Serial samples of cerebrospinal fluid from one infant showed a peak concentration two weeks after the haemorrhage.

Posthaemorrhagic ventricular dilatation (PHVD) occurs after intraventricular haemorrhage (IVH) in preterm infants and is assumed to be caused by small particles of blood clot obstructing the flow of cerebrospinal fluid through the ventricular system, basal cisterns, and arachnoid villi on the surface of the cerebral hemispheres. Little is known about the natural mechanisms by which the body clears clots from the cerebrospinal fluid. Masuda *et al* concluded that fibrinolytic activity started to increase three to five days after experimental intracerebral haematoma and increased for seven to 10 days, decreasing after 21 to 28 days.[1] We have carried out a study to determine whether there is evidence of natural fibrinolysis in the cerebrospinal fluid after IVH.

Patients and methods

COLLECTION OF SAMPLES OF CEREBROSPINAL FLUID

Normal preterm infants
Because of clinical instability, five preterm infants underwent lumbar puncture (one on two occasions) to exclude infection; they were subsequently found to be free from both infection and intraventricular haemorrhage. For ethical reasons completely healthy infants could not be subjected to lumbar puncture purely for research purposes.

Intraventricular haemorrhage
Four preterm infants with IVH (without PHVD) visible on cranial ultrasound scan underwent lumbar puncture to exclude infection.

Intraventricular haemorrhage progressing to PHVD
The definition of PHVD was 'ventricular width expanding after IVH to 4 mm over the 97th centile' which was the same definition as that used in the multicentre trial of early tapping[2] and in a textbook of neonatal neurology.[3] Five preterm infants required repeated tapping to control cerebrospinal fluid pressure and excessive head growth. After the first therapeutic lumbar or ventricular tap, fluid was kept frozen for analysis of cross linked fibrin degradation products. In one infant, who had eight lumbar punctures (either for diagnostic or therapeutic purposes) a sample of fluid from each lumbar puncture was kept for analysis of concentrations of cross linked fibrin degradation products.

MEASUREMENT OF FIBRINOLYTIC ACTIVITY

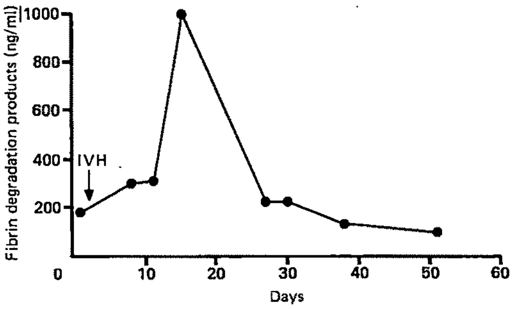
Assays of cross linked fibrin degradation products
This assay was performed directly on cerebrospinal fluid using the procedure described by Gaffney *et al*,[4] with the following modification. The polyvinyl plates were coated with a catcher monoclonal antibody, mab NIBn-123 (10 µg/ml), which has a similar specificity to the monoclonal antibody used in the original assay; a detector (tag) polyclonal antibody to human fibrinogen (Dakopatts), which was labelled with horseradish peroxidase, was also used. Sensitivity of the assay was in the range 3–5000 ng/ml.

Results

The table shows that after IVH the concentra-

Median concentrations of cross linked fibrin degradation products in cerebrospinal fluid in normal infants and those with IVH and PHVD

	No of infants	*Cross linked fibrin degradation products (ng/ml)*	
		Median	*Range*
Normal preterm infants	5	102	20–252
IVH	4	315	280–410
PHVD	5	1000	405–5000



Serial concentrations of cross linked fibrin degradation products in the cerebrospinal fluid of an infant who developed posthaemorrhagic ventricular dilatation and was treated by serial tapping.

tions of cross linked fibrin degradation products were considerably higher than in the 'normal' preterm infants. In the five infants who developed PHVD, the concentrations were even higher than in those with haemorrhage alone. The figure shows the serial concentrations in an infant who developed PHVD after IVH, which resolved after repeated lumbar punctures. It can be seen that the concentrations peaked at about two weeks.

Discussion

These preliminary investigations show that preterm infants actively attempt to lyse blood clot in the cerebrospinal fluid. There is some evidence of fibrinolytic activity in 'normal' infants but this is increased in those who have had an intraventricular haemorrhage. Larger haemorrhages that lead on to ventricular dilatation seem to elicit a greater fibrinolytic response. The peak of fibrinolysis after about two weeks in the infant whose results are shown in the figure confirms the fibrinolytic peak found by Masuda *et al.*[1] We found no evidence to suggest that the infants who developed PHVD had decreased fibrinolytic activity.

We are currently investigating the possibility of preventing PHVD by increasing intraventricular fibrinolysis.

1 Masuda T, Dohrmann GJ, Kwaan HC, Erickson RK, Wollman RL. Fibrinolytic activity in experimental intracerebral hematoma. *J Neurosurg* 1988;68:274–8.
2 Ventriculomegaly Trial Group. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. *Arch Dis Child* 1990;65:3–10.
3 De Vries LS, Larroche JC, Levene MI. Intracranial sequelae. In: Levene MI, Bennett MJ, Punt J, eds. *Fetal and neonatal neurology and neurosurgery*. Edinburgh: Churchill Livingstone, 1988:346–52.
4 Gaffney PJ, Creighton LJ, Perry MJ, Callus M, Thorpe R, Spitz M. Monoclonal antibodies to crosslinked fibrin degradation products (XL FDP). *Br J Haematol* 1988;68:83–90.

Erythropoietin responsive progenitors in anaemia of prematurity

A J B Emmerson, N B Westwood, R A Rackham, C M M Stern, T C Pearson

United Medical and Dental Schools of St Thomas's and Guy's Hospitals, St Thomas's Campus, London SE1 7EH
Department of Neonatal Paediatrics
A J B Emmerson
C M M Stern
Department of Haematology
N B Westwood
R A Rackham
T C Pearson

Correspondence to:
Dr Emmerson.

Accepted 30 January 1991

(*Arch Dis Child* 1991;66:810–811)

Abstract

Circulating erythroid progenitors (BFU-E) in five anaemic preterm infants (haemoglobin<100 g/l) were about 2 and 4·4 times as abundant as in 10 preterm infants who were not anaemic and five healthy adults, respectively, and were significantly more responsive to low concentrations of recombinant human erythropoietin (rHuEpo) than those from healthy adults. These results encourage further studies in the use of rHuEpo for the treatment of the anaemia of prematurity.

There is interest in the use of recombinant human erythropoietin (rHuEpo) for the prevention and treatment of anaemia of prematurity, which is an hyporegenerative anaemia associated with low concentrations of erythropoietin.[1] The clinical efficacy of this hormone for the treatment of anaemic premature infants has not yet been shown, though one uncontrolled study suggests that it may increase the packed cell volume.[2]

Progenitors committed to the erythroid line can be recognised in cell culture systems. These are of two types: the primitive progenitor, the erythroid burst forming unit (BFU-E), which is found in the peripheral circulation, and the more mature progenitor, the erythroid colony forming unit (CFU-E), which is predominantly found in bone marrow. In this study we report the relative numbers of BFU-E progenitors in infants with the anaemia of prematurity, and their response to various doses of rHuEpo, compared with those of progenitors that are present in healthy adults and cord blood from term infants.

Patients and methods

Two millilitres of venous blood were drawn into preservative free heparin from each of 10 premature infants who were not anaemic and five who were anaemic (haemoglobin <100 g/l). Five cord blood samples from normal term infants and samples from 10 healthy adult volunteers were collected for comparison. The progenitors were separated by centrifugation over a Ficoll metrizoate density barrier (1077 g/l); 1×10^5 cells from the light density cell fraction were cultured for 14 days at 37°C under 5% carbon dioxide in air in a serum free culture medium with a 2·2% methyl cellulose base, and containing Iscove's modified Dulbecco's medium, bovine serum albumin, cholesterol, sodium pyruvate, transferrin, 1-glutamine, nucleosides, insulin, inorganic salts, and antibiotics.[3] This system had previously been validated in our laboratory for the growth of erythroid progenitors in blood samples from premature infants (submitted for publication).

Six doses of rHuEpo from 0–2IU were added to the culture dishes containing a total volume of 1 ml, and all cultures were done in duplicate. The BFU-E were counted through an Olympus CK2 tissue culture microscope and the number of circulating erythroid progenitors was derived from the dishes containing 2IU/ml of rHuEpo. The significance of differences was assessed by Wilcoxon's rank sum test. Ethical approval was given by the local ethics committee.

The baseline measurements for the premature infants are shown in table 1. All infants were well and were not being ventilated. No blood transfusions had been given within a week of the blood samples being taken.

Results

The results show that in the five infants with anaemia of prematurity there were 4·4 times the concentration of circulating erythroid progenitors found in normal healthy adults (p=0·01, table 2). There are twice the number of circulating BFU-E progenitors in anaemic infants (35·5) than in infants who were not anaemic (17·5) although this is not significant.

In addition, neonatal progenitors respond at least as well to rHuEpo as those from adult or cord blood (figure). At the low concentrations of 0·1 and 0·5 IU/ml of rHuEpo there is a significant difference between the responsiveness of progenitors from anaemic preterm infants and those from healthy adults (p=0·05).

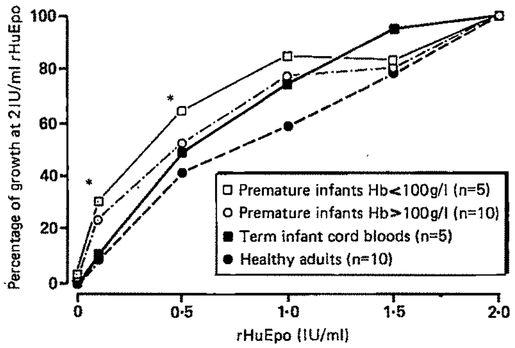
Table 1 Characteristics of the preterm infants studied. Values are expressed as mean (SD)

	Anaemic infants (n=5)	*Infants not anaemic (n=10)*
Gestational age (weeks)	31·1 (2·2)	29·7 (3·9)
Age at time of study (days)	35·4 (15·6)	27·2 (17·7)
Birth weight (g)	1670 (450)	1440 (450)
Haemoglobin concentration (g/l)	88 (9)	143 (33)

Table 2 Median (upper and lower quartile) numbers of circulating erythroid progenitors (BFU-E)/10^5 mononuclear cells at 2IU/ml recombinant erythropoietin

Subjects	*Median (quartiles)*
Anaemic infants (n=5)	35·5 (17·4–52·4)*
Infants not anaemic (n=10)	17·5 (8·5–21·9)
Cord blood from term infants (n=5)	10·5 (8·5–11·0)
Healthy adults (n=10)	8·0 (2·0–17·0)

*p=0·01 compared with healthy adults.



*Recombinant human erythropoietin (rHuEpo) dose response curves for circulating erythroid progenitors (BFU-E) from peripheral blood samples from anaemic preterm infants with haemoglobin (Hb) concentrations of <100 g/l and non-anaemic preterm infants, cord blood from term infants, and healthy adult volunteers; *p=0·05 for difference between the results for preterm infants and healthy adults.*

There is no significant difference at concentrations of rHuEpo of 1 IU/ml and above.

Discussion

The most important factor that affects the growth and development of the erythroid line is erythropoietin. Since the characterisation of rHuEpo by Jabobs *et al*,[4] and its commercial production, many therapeutic roles have been suggested for it. The high incidence of anaemia of prematurity, which has considerable morbidity, and the reported low concentrations of endogenous erythropoietin,[1] imply that this hormone may be a possible alternative treatment for the anaemia of prematurity.

The current treatment of transfusion with adult blood is unsatisfactory as there are many complications, including the risk of transmission of infective agents (especially cytomegalovirus), difficulties of venous access, and the further suppression of natural erythropoiesis.[5] An alternative treatment that would reduce or prevent the requirement for transfusion would be welcomed.

Rhondeau *et al* have reported dose response curves for the erythroid progenitor that is mainly found in bone marrow, CFU-E, and has shown that the CFU-E from the marrow of premature infants are as responsive to rHuEpo as those from cord blood from term infants and from healthy adult marrow. The present studies show both a significant increase in the numbers of circulating erythroid progenitors in anaemic premature infants, and an increased responsiveness of these progenitors to rHuEpo compared with adult BFU-E. These findings lend weight to the suggestion that there may be a role for the clinical use of rHuEpo in the prevention or treatment of anaemia of prematurity.

1 Stockman JA III, Graeber JE, Clark DA, McClellan K, Garcia JF, Kavey REW. Anaemia of prematurity: determinants of the erythropoietin response. *J Pediatr* 1984;**105**: 786–92.
2 Halpérin DS, Wacker P, Lacourt G, *et al*. Effects of recombinant human erythropoietin in infants with the anaemia of prematurity: a pilot study. *J Pediatr* 1990;**116**: 779–86.
3 Migliaccio G, Migliaccio R. Cloning of human erythroid progenitors (BFU-E) in the absence of fetal bovine serum. *Br J Haematol* 1987;**67**:129–33.
4 Jacobs K, Shoemaker C, Rudersdorf R, *et al*. Isolation and characterisation of genomic and cDNA clones of human erythropoietin. *Nature* 1985;**313**:806–10.
5 Lang DJ, Valeri CR. Hazards of blood transfusion. *Adv Pediatr* 1977;**24**:311–38.
6 Rondeau SM, Christensen RD, Ross MP, Rothstein G, Simmons MA. Responsiveness to recombinant human erythropoietin of marrow erythroid progenitors from infants with the anaemia of prematurity. *J Pediatr* 1988; **112**:935–40.

Archives of Disease in Childhood 1991; 66: 812–815

OBSTETRICS FOR PAEDIATRICIANS

Preterm prelabour rupture of membranes

David James

Bristol Maternity Hospital,
Southwell Street,
Bristol BS2 8EG

Correspondence to:
Dr James.

The problem

Unfortunately there are too many examples in obstetrics of very important conditions for which there is no consensus of professional opinion about definition, diagnosis, risks, and above all, management. Preterm prelabour rupture of the membranes (PPROM) is such a case.

The best, most widely used, and simplest definition of PPROM is membrane rupture occurring before the onset of regular uterine contractions prior to 37 weeks' gestation. Some authors add caveats, for example, about the interval between membrane rupture and the onset of labour or not including cases above 34 weeks' gestation. In general, these are unhelpful modifications to the definition. However, while not helpful for definition, these two factors—duration of membrane rupture and gestational age—critically influence the risks and management of PPROM.

The reported incidence of prelabour membrane rupture in all pregnancies varies from 1–10% depending on the population studied. However, if elective preterm deliveries and fetal death before labour are excluded, the incidence of PPROM in women delivering preterm is between 40–60%. The main independent risk factors for PPROM are antepartum vaginal bleeding, maternal smoking, and previous preterm delivery.

The aetiology and pathogenesis of PPROM are poorly understood. For example, it is not clear whether pregnancies complicated by spontaneous preterm labour and delivery *with* PPROM should be regarded as different in these respects from cases *without* preceding membrane rupture. Factors claimed to be possible causes of PPROM include infection, membrane collagen abnormalities, cervical incompetence, raised intrauterine pressure, and low membrane calcium and magnesium content. There have been many theories of the mechanisms whereby these factors produce PPROM with much research currently involving platelet activating factor and prostaglandin metabolism in the membranes. As with most aspects of spontaneous preterm delivery, the explanation remains as elusive as ever.

While the causes of PPROM are uncertain the risks are well known. The three serious complications, in order of importance, are preterm labour and delivery and its consequences, infection, and pulmonary hypoplasia. Other important complications are various deformities due to oligohydramnios, placental abruption, cord compression (either due to cord prolapse or severe oligohydramnios), and mechanical difficulties at delivery. There is no information to indicate whether these risks are any different for 'hindwater' as opposed to 'forewater' PPROM thus in practice no distinction is made between the two.

The problem of diagnosis

The diagnosis of membrane rupture is not difficult if there is liquor gushing from the vagina or the cervix on sterile speculum examination. However, in many instances this is not the case. A careful history is important, with special care being taken to distinguish PPROM from urinary incontinence. The presence of white flecks (vernix) or green coloration (meconium) of the the liquor may be a useful feature in the history. However, vernix and meconium are characteristic of term liquor and seldom found before 32 weeks. If a sample of fluid is available for examination then it may be possible to decide whether it is liquor. Amniotic fluid contains protein and produces a typical fern like pattern when allowed to dry on a microscope slide; urine does not, but in contrast contains creatinine and uric acid. The pH of liquor, at 7·1–7·3, tends to be higher than that of urine.

A variety of tests have been developed specifically to distinguish liquor not only from urine but also from vaginal secretions and other fluids, but they all have limitations. Some, including the ferning test, are of little value at preterm gestations. For example, the Nile blue test, which produces a positive result by detecting the presence of orange staining anucleate cells in liquor, has a false negative rate of 90% at 36 weeks and 99% at 32 weeks. Detection of α fetoprotein using monoclonal antibodies should be more accurate at preterm gestations; however, it has not yet been adequately evaluated in clinical practice. The nitrazine test is probably the most widely used. The underlying principles are that nitrazine solution changes from yellow-green to dark blue at a pH of 6·5 or more and while vaginal pH during pregnancy is normally between 4·5–6·0 that of liquor is usually alkaline. Unfortunately nitrazine can also turn blue when exposed to tap water, certain antiseptic solutions, cervical mucus, semen, blood, and alkaline urine.

The transabdominal injection of various dyes in order to ascertain whether they appear through the cervix as an invasive method of diagnosing membrane rupture is not without risk for the fetus and is not widely practised.

Ultrasound evaluation of liquor volume has merit in theory. The presence of oligohydramnios on scan with a history suggestive of membrane rupture would probably correctly confirm the diagnosis. However, in practice ultrasound is of limited value. To produce appreciable oligohydramnios on ultrasound, the clinical features are usually clear cut with liquor leak continuing and oligohydramnios being obvious on abdominal palpation. In contrast, the commoner clinical dilemma is where there has possibly been a small leak which has stopped. In such cases ultrasound will not detect the small reduction of liquor volume.

The problem of preterm delivery

Preterm labour and delivery and its complications (respiratory distress syndrome, intraventricular haemorrhage, and chronic lung disease) are the most common and important consequences of PPROM. Approximately 60% of cases will go into labour within one week of PPROM at 24 weeks' gestation or less; this figure rises to 80% after 34 weeks.

Because of the difficulties in accurate early diagnosis of intrauterine infection (see below) clinical management has concentrated on trying to assess the consequences of preterm delivery especially when PPROM occurs before 34 weeks. Almost exclusively the evaluation has centred on fetal pulmonary maturity and the likelihood of respiratory distress syndrome. In this regard the traditional lecithin:sphingomyelin ratio in amniotic fluid has proved unreliable, especially when the liquor has been collected vaginally. Fortunately, phosphatidylglycerol is not found in any other body fluids than mature lung surfactant and thus its estimation is the test of choice in such circumstances. Of course, demonstration of fetal lung maturity does not necessarily mean that other consequences of preterm delivery will not occur and that early elective delivery should be automatically undertaken. Arguably the main value of demonstrating fetal surfactant production is that maternal administration of steroids can be avoided (see below). At present the timing of elective delivery in PPROM even with fetal lung maturity is a matter of clinical judgment rather than on the basis of properly conducted randomised trials. In practice, most clinicians tend to be more conservative the more preterm the pregnancy and opt for elective delivery only after 34 weeks.

The problem of infection

The early diagnosis of intrauterine infection in PPROM is important yet difficult. The classical signs of maternal fever, maternal and fetal tachycardia, a tender uterus, and foul smelling liquor are probably relatively late features. Furthermore intrauterine infection is not the only explanation of maternal fever or maternal or fetal tachycardia. Another confounding factor is that the discharge from fulminating aerobic infection may be inoffensive.

A number of laboratory methods have been introduced in an attempt to achieve earlier diagnosis of intrauterine infection with PPROM. In general they have proved unreliable. A summary of the tests is given in the table. Gram stain, white cell count, and culture of the liquor is probably the best of those available. But from where should the liquor be obtained for this bacterial examination? Collecting it vaginally is easier and identifying certain fetal pathogens such as group B streptococci, *Escherichia coli*, or bacteriodes, especially if single isolates, may be important. However, the usefulness of finding such organisms in planning subsequent management is not known. Negative cultures, on the other hand, are reassuring. Because of this dilemma of possible vaginal commensals contaminating liquor collected via that route, obtaining liquor by amniocentesis has been advocated to allow a more specific diagnosis of intrauterine infection. Unfortunately, there is no evidence to show that this approach is more accurate at diagnosing intrauterine infection. Furthermore, liquor is not obtained in 30–50% of cases and the procedure carries a risk to the fetus of trauma and the introduction of infection.

Of more recent interest are the observations that early intrauterine infection appears to be associated with disturbances in fetal behavioural physiology. Abnormalities of fetal heart rate monitoring (cardiotocography) and the fetal biophysical profile (concurrent recording of fetal heart rate, breathing, movements, tone, and liquor volume) correlate closely with proved intrauterine sepsis. These non-invasive tests have obvious advantages over amniocentesis. However, at present it is not known whether use of these tests will prove to be helpful in determining the appropriate management and improving fetal outcome.

There is a widely held view that vaginal examinations in PPROM introduces or causes infection. Although there is a reported association of vaginal examinations and the development of sepsis, there are no controlled data to confirm or refute the view that this relationship is causal. There is no evidence as to whether

Accuracy of prediction of intrauterine infection by laboratory tests in published studies (extracted from Ohlsson and Wang[4]). Results are shown as range

Test	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
(1) White cell count, band count (%)	23–80	61–98	40–75	40–91
(2) C reactive protein (%)	37–100	44–100	10–100	50–100
(3) Gram stain, white cells, and culture of liquor (%)	36–80	83–98	78–87	56–92
(4) Leucocyte esterase (%)	8–83	84–100	4–100	68–92
(5) Gas chromatography (%)	29–93	56–91	20–88	67–96

Decimal places are omitted for clarity. The definition of 'intrauterine infection' varied.

digital or speculum examination is better. In general there are two alternative practices. Firstly, a sterile examination is performed on all cases of PPROM at presentation, though there are then differences of opinion as to how frequently examinations should be subsequently repeated. In contrast, other obstetricians maintain that vaginal examinations should be carried out with PPROM only in active labour. There is no evidence to suggest which approach is superior. What is clear, however, is that vaginal examination should only be undertaken to obtain information that is unavailable by other means.

The problem of pulmonary hypoplasia

Preterm delivery is numerically the most important complication of PPROM but pulmonary hypoplasia due to oligohydramnios is in many ways more distressing. The prognosis for respiratory distress syndrome in the preterm baby delivering after PPROM and after 28 weeks' gestation is very good with over 90% survival rates due to measures such as ventilatory support and exogenous surfactant treatment. Pulmonary morphological development can be impaired with very preterm membrane rupture especially before 26 weeks. Thus a mother might spend weeks in hospital, the membranes having ruptured before 26 weeks, only for the baby to be delivered, perhaps after 30 weeks, and dying from pulmonary hypoplasia. Theories of the pathogenesis of the condition include fetal compression reducing lung growth, decreased fetal breathing, and excessive loss of lung fluid.

The problem before birth is that there is no reliable way of diagnosing pulmonary hypoplasia. Fetal breathing movements, chest wall growth, and liquor volume measurements have all been advocated but all have limitations. In practice, an expectant approach is followed even if there is a strong suspicion that the condition may be likely to develop. For example, with membrane rupture early in the second trimester, continued fluid loss, and severe oligohydramnios then pulmonary hypoplasia is highly probable but not every case will result in the problem.

Amnioinfusion (restoration of the amniotic fluid volume with, for example, N-saline) is an alternative approach to the problem currently under evaluation. Although there is evidence that such an approach may reduce caesarean section rates, fetal heart abnormalities, and fetal acid-base status in the presence of PPROM, it is not clear whether the overall outlook for the fetus is any better. The outcome of randomised controlled trials is awaited.

The problem of management

Since preterm labour and delivery are the main risks of PPROM, referral to a centre with facilities for neonatal intensive care, if these are not available locally, is generally accepted as wise management. There is, however, less agreement over other aspects of management of PPROM. Furthermore, a review of the published evidence from controlled studies is complicated by factors such as the heterogeneous nature of study groups, possible selection bias, small numbers, uncontrolled and variable concomitant treatment. Some generalisations are possible, however.

There is no consistent evidence that the use of prophylactic antibiotics in PPROM reduces maternal infection risk before delivery, increases neonatal sepsis risk after delivery, or significantly prolongs pregnancy. The only proved benefit is that maternal infection rates after delivery are significantly reduced by antibiotic prophylaxis. These observations together with the largely theoretical rather than proved consequences of the development of resistant strains and masking of infection in the newborn are probably the reasons for many authors not supporting the routine use of prophylactic antibiotics in PPROM.

There is no proved benefit from the use of oral tocolytics in PPROM. The few comparative studies that have been published suggest a nonsignificant lower incidence of delivery within 48 hours with their use but any such suggestion of benefit is lost when delivery rates at 10 days after PPROM are compared.

There have been several trials of the use of maternally administered corticosteroids, such as dexamethasone, in PPROM and all have demonstrated a clear advantage of the treatment. Overall, treatment with such agents significantly reduced the risk of development of respiratory distress syndrome by approximately 50%. However, in addition all the studies did demonstrate a trend to slightly higher neonatal sepsis rates, though this was not statistically significant. The conclusion from such work is that the benefits of corticosteroids would seem to outweigh the risks.

Comparative studies have been made of 'active approach' to delivery, namely inducing labour after corticosteroid treatment or as soon as there is evidence of fetal lung maturity, with the 'conservative approach' of waiting to a much later gestation such as 34 weeks before inducing labour or until spontaneous labour occurs. There are consistent trends in the published reports of higher rates of maternal sepsis, caesarean section, neonatal sepsis, respiratory distress syndrome, and neonatal mortality with the 'active' policy of early induction of labour and it would seem that it confers more harm than benefit.

When spontaneous labour occurs after PPROM the correct approach is to allow it to proceed. There is circumstantial evidence to suggest that the event itself may be a manifestation of 'subclinical' intrauterine infection. There is no evidence of benefit to mother or baby from the use of tocolytics in this circumstance. The only exception to this view might be where uterine activity commences at a nonviable gestation such as below 24 weeks. However, there are no studies that have addressed this issue and if this approach is followed because 'there is nothing to lose', great vigilance must be maintained for infection. When spontaneous labour occurs after PPROM and there is evidence of infection delivery must be allowed to proceed. The chosen mode of delivery would be that appropriate for any equivalent preterm fetus without PPROM. That said, the issue of which is the best method for delivery of the preterm fetus presenting by the breech is not resolved. Furthermore, there is some evidence that in the presence of infection caesarean section may carry a higher morbidity than vaginal delivery. Though there are no trials of the use of antibiotics before delivery in the presence of infection commonsense argues for their use as the objections are largely theoretical.

Conclusions

Although there are more divergent opinions over the management of PPROM than the scientific evidence can support, the following general guidelines are suggested:

(1) Accurate diagnosis and gestational age estimation are important at the outset.

(2) Transfer to a tertiary referral centre should be considered if local facilities for neonatal intensive care are not adequate.

(3) Prolongation of the pregnancy to 32–34 weeks (rather than active delivery after steroid treatment or evidence of fetal lung maturity) should be the aim.

(4) Surveillance should be maintained for: (a) intrauterine sepsis—with regular maternal pulse and temperature recordings, fetal heart rate, and behaviour monitoring and regular examination of liquor collected vaginally (Gram stain, leucocyte count and culture); (b) fetal compromise—not just from infection but from cord compression using the same regular monitoring techniques as for sepsis; and (c) uterine activity.

(5) Corticosteroid administration confers more benefit than harm, but the routine use of tocolytics or prophylactic antibiotics is not recommended.

(6) Vaginal examinations should be kept to a minimum and only be used where the information to be gleaned cannot be obtained by any other means.

(7) Where infection occurs intravenous antibiotics should be used and delivery by the normal route for that stage of pregnancy should be undertaken.

Finally, further research is needed in the following areas:

(1) The relative risks of hindwater versus forewater membrane rupture.

(2) More accurate methods of diagnosing intrauterine infection.

(3) The use of prophylactic antibiotics in a selective manner (for example, with concurrent administration of corticosteroids).

(4) Amnioinfusion.

Suggestions for further reading

1 Keirse MJNC, Ohlsson A, Treffers PE, Kanhai HHH. Prelabour rupture of the membranes preterm. In: Chalmers I, Enkin M, Keirse MJNC eds. *Effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1989: 666–93.

2 Kilbride HW, Yeast JD, Thibeault DW. Intrapartum and delivery room management of premature rupture of membranes complicated by oligohydramnios. *Clin Perinatol* 1989;**16**:863–88.

3 Ohlsson A. Treatments of preterm premature rupture of the membranes: a meta-analysis. *Am J Obstet Gynecol* 1990; **162**:890–906.

4 Ohlsson A, Wang E. An analysis of antenatal tests to detect infection in preterm premature rupture of the membranes. *Am J Obstet Gynecol* 1989;**160**:809–18.

Archives of Disease in Childhood 1991; **66**: 816–822

CURRENT PRACTICE

Antenatal diagnosis of inborn errors of metabolism

M A Cleary, J E Wraith

Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA
M A Cleary
J E Wraith

Correspondence to: Dr Wraith.

The introduction of experimental treatment for lysosomal storage disorders and the increasing understanding of the molecular defects behind many inborn errors have overshadowed the fact that for many affected families the best that can be offered is a rapid, accurate prenatal diagnostic service. Many conditions remain at best only partially treatable and as a consequence the majority of parents seek antenatal diagnosis in subsequent pregnancies, particularly for those disorders resulting in a poor prognosis in terms of either life expectancy or normal neurological development.

The majority of inborn errors result from a specific enzyme deficiency, but in some the primary defect is in a transport system or enzyme cofactor. In some conditions the biochemical defect is limited to specific tissues only and this serves to restrict the material available for antenatal diagnosis for these disorders. Fortunately for many inborn errors the metabolic defect is generalised and both amniotic and chorion villus cells can be used as a diagnostic tissue.

Before contemplating prenatal diagnosis it is essential that a firm biochemical diagnosis has been established in the index case. It is unsafe to rely only on a clinical or histological diagnosis as many of the inherited disorders share a similar phenotype. To ease interpretation of results obtained on the fetus it is necessary to know the heterozygote levels of enzyme activity in the parents; occasionally these are remarkably low and can lead to difficulties in ascribing fetal genotype.

The properties of some enzymes are appreciably different when studied at different times of gestation. In addition, the activity obtained from chorion villus material may be very different from that obtained on amniotic fluid cells. It is essential that the correct tissue is collected at the most appropriate time. Liaison with the laboratory staff performing the test is mandatory if mistakes are to be avoided.

Prenatal testing by analysis of fetal DNA by either a gene specific DNA probe or gene tracking using restriction fragment length polymorphisms (RFLPs) requires proband DNA for comparison. This underlies the importance of establishing fibroblast cultures from all patients diagnosed as having a metabolic disorder as well as ensuring that blood is taken from all relevant family members for DNA extraction and storage.

Most prenatal testing for metabolic disease is performed in a few specialised laboratories.

Sample requirement and techniques used in prenatal diagnosis

By far the majority of antenatal diagnoses are performed on samples obtained by either amniocentesis or chorion villus biopsy. For some disorders, however, the defect is not detectable in this material and more invasive methods have been applied to obtain a diagnostic sample.

FETAL LIVER BIOPSY

Fetal liver biopsy has been performed to diagnose ornithine carbamoyl transferase deficiency and primary hyperoxaluria type 1. Glucose-6-phosphatase deficiency (glycogen storage disease type I) could also be detected by this method. The technique, however, is invasive and can be performed by only a few highly specialised fetal diagnostic units.

FETAL BLOOD SAMPLING

Fetal blood sampling could be used for the antenatal diagnosis of many inborn errors. The sample, however, tends to be collected late in pregnancy and the technique is probably best reserved as a back up in case of failed amniotic fluid cell culture.

AMNIOCENTESIS

Amniocentesis has been the most common procedure for antenatal diagnosis of metabolic disease. Both the cell free amniotic fluid and cultured and uncultured amniotic fluid cells are useful in diagnosis.

The procedure is usually performed at 15–16 weeks' gestation and most analyses can be performed within two to three weeks of culture. First trimester amniocentesis has been attempted to allow earlier diagnosis, but the smaller sample size and possible variation in enzyme activity at the earlier stage of pregnancy have introduced variables that need to be studied before the technique can be widely applied.

(1) Cell free amniotic fluid can be used to detect a number of intermediary metabolites in many inborn errors. Where possible this technique should be backed by specific enzyme analysis, but for many conditions does allow a quick diagnosis. It is particularily relevant for organic acid disorders using stable isotope dilution gas chromatography with mass spectrometry and selected ion monitoring.

In mucopolysaccharide disorders the pattern of excess glycosaminoglycan excretion can be detected by two dimensional electrophoresis and this can form the basis of a reliable antenatal test for this group of conditions.

(2) Amniotic fluid cells in culture are a common material used in antenatal diagnosis. In most cases the enzyme activity obtained in this tissue mirrors that obtained in cultured skin fibroblasts. As well as direct enzyme assay, radiolabelled incorporation studies can be performed on the cultured cells and a wide range of disorders detected. Contamination by mycoplasma or other organisms is the biggest threat to antenatal diagnosis by this method.

CHORION VILLUS BIOPSY

Chorion villus biopsy offers the advantage of first trimester diagnosis. Direct analysis of enzyme activity on fresh uncultured villus tissue usually allows a result to be available within 24–48 hours of the procedure. Problems associated with the technique include the possibility of maternal contamination and differences in enzyme activity in this tissue as compared with skin fibroblasts or cultured amniotic fluid cells. Despite these possible limitations most prenatal diagnoses for inborn errors are performed on chorion villus samples.

Specific inborn errors of metabolism

The appendix lists the specific inborn error, the biochemical defect, chromosome location of the gene mutation where known, and the test used for antenatal diagnosis. Where antenatal diagnosis has been successfully achieved the method used is clearly shown. For some disorders prenatal diagnosis is theoretically possible, although to the authors' knowledge not as yet successfully performed. In this case the most likely tissue and method are indicated with the rider, 'possible'. The key to the abbreviations used is shown at the end of the appendix.

Appendix

Specific inborn errors of metabolism

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(A) CARBOHYDRATE METABOLISM			
(i) Galactose			
Galactokinase deficiency	Galactokinase	17q21-q22	AF, CVB
'Classical' galactosaemia	Galactose-1-phosphate-uridyl transferase	9p13	AF, CVB
Epimerase deficiency	UDP-Galactose-4-epimerase	1pter-p32	Poss CC
(ii) Fructose			
Hereditary fructose intolerance	Aldolase B	9q22	Poss DNA
Fructose 1–6 bisphosphatase deficiency	Frutose 1–6 bisphosphatase	—	No
(iii) Glycogen storage disease			
Ia Von Gierke	Glucose-6-phosphatase	—	Poss FT
b	Glucose-6-phosphatase translocase (T_1)	—	Poss FT
c	Glucose-6-phosphatase translocase (T_2)	—	Poss FT
II Pompe	Lysosomal acid glucosidase	17q23	AF, CVB
III Debrancher enzyme deficiency	Amylo-1-6-glucosidase	—	AF, CVB
IV Brancher enzyme deficiency	1-4-Glucan 6-glycosyl-transferase	—	AF, CVB
V McCardle	Muscle phosphorylase	11q13-qter	No
VI Liver phosphorylase deficiency	Liver phosphorylase	14	Poss FT
VII Phosphofructokinase deficiency	Phosphofructokinase	1cen-q32	No
IXa Phosphorylase kinase (recessive)	Phosphorylase kinase	16q12–q13·1	Poss FT
IXb Phosphorylase kinase (X linked)	Phosphorylase kinase	Xq12–q13	Poss FT
(B) AMINO ACID METABOLISM			
(i) Phenylalanine			
'Classical' phenylketonuria	Phenylalanine hydroxylase	12q22–q24·1	DNA
Tetrabiopterin homoeostasis	Dihydropteridine reductase	4p15·3	AF, CVB
Tetrabiopterin synthesis	Guanosine triphosphate cyclohydrolase	—	MET
	6-Pyruvoyltetrahydropterin synthase	—	MET

Condition	**Enzyme deficiency**	**Chromosome location**	**Prenatal diagnosis**
(ii) Methionine			
Homocystinuria	Cystathionine synthase	21q22–q22·1	AF, CVB
(iii) Tyrosine			
Tyrosinaemia I	Fumarylacetoacetate hydrolase	15q23–q25	AF, CVB
Tyrosinaemia II	Tyrosine aminotransferase	16q22–q22·1	No
(iv) Valine, leucine, isoleucine			
Maple syrup urine disease	Branched chain ketoacid dehydrogenase	19q13·1–q13·2	AF, CVB
(v) Glycine			
Non-ketotic hyperglycinaemia	Glycine cleavage system	9p22	CVB
(vi) Lysine			
Hyperlysinaemia	Aminoadipic semialdehyde synthase	—	UNK
(vii) Proline			
Hyperprolinaemia I	Proline oxidase	—	UNK
Hyperprolinaemia II	Pyrroline-5-carboxylate dehydrogenase	—	UNK
Hyperimidodipeptiduria	Prolidase	19q12–q13·2	Poss CC
(viii) Ornithine			
Gyrate atrophy of the choroid and retina	Ornithine aminotransferase	10q26	Poss CC
Hyperornithinaemia-hyperammonaemia-homocitrullinaemia (HHH syndrome)	Basic defect unknown	—	No
(C) UREA CYCLE DISORDERS			
N-acetylglutamate synthetase deficiency	N-acetylglutamate synthetase	—	UNK
Carbamyl phosphate synthetase deficiency (CPS)	Carbamyl phosphate synthetase	2p	Poss DNA/FT
Ornithine carbamyltransferase deficiency (OCT)	Ornithine carbamyltransferase	Xp21·1	Poss DNA/FT
Citrullinaemia	Argininosuccinic acid synthetase	9q34	AF, CVB
Argininosuccinic aciduria (ASA)	Argininosuccinate lyase	7p21-cen	AF, CVB
Argininaemia	Arginase	6q23	Poss DNA/FT
(D) ORGANIC ACID DISORDERS			
(i) Propionate and methylmalonate metabolism			
Propionic acidaemia	Propionyl-CoA carboxylase:		
	α-subunit	13	AF, CVB
	β-subunit	3q13·3–q22	AF, CVB
Multiple carboxylase deficiency	Holocarboxylase synthetase	—	MET
	Biotinidase	—	MET
Methylmalonic acidaemia	Methylmalonyl-CoA mutase	6p12-p21·2	AF, CVB
	Adenosylcobalamin synthesis:		
	cblA	—	AF, CVB
	cblB	—	AF, CVB
	(see also cobalamin metabolism)		
(ii) Pyruvate and lactate metabolism			
Lactate dehydrogenase deficiency	Lactate dehydrogenase	11p15·4	UNK
Pyruvate dehydrogenase deficiency	Pyruvate dehydrogenase complex:		***
	E_1 (decarboxylase) component	α-Xp22·1–22·2	Poss DNA
		β-3p13-q23	
	E_2 (dihydrolipoyl transacylase)	—	
	E_3 (dihydrolipoyl dehydrogenase)	7p15–q35	
	Pyruvate dehydrogenase phosphatase	—	
Pyruvate carboxylase deficiency	Pyruvate carboxylase	11q	AF
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	—	UNK

Condition	**Enzyme deficiency**	**Chromosome location**	**Prenatal diagnosis**
(iii) Respiratory transport chain defects			
The components of the respiratory transport chain are composed of many polypeptide subunits some of which are encoded by mitochondrial DNA			
Complex I	NADH CoQ reductase		###
Complex II	Succinate CoA reductase		
Complex III	$CoQH_2$-cyt c reductase		
Complex IV	Cytochrome oxidase		AF, CVB
Complex V	Oligomycine sensitive ATPase		
(iv) Branched chain organic acidaemias			
Isovaleric acidaemia	Isovaleryl-CoA dehydrogenase	15q14–q15	MET, AF
Isolated 3-methyl crotonyl CoA carboxylase deficiency	3-Methylcrotonyl carboxylase	—	Poss CC
3-Methylglutaconic aciduria	3-Methylglutaconic hydratase	—	Poss CC
3-Hydroxy-3-methylglutaryl CoA lyase deficiency	3-Hydroxy-3-methylglutaryl-CoA lyase	AF, CVB —	
Mevalonic aciduria	Mevalonate	—	AF
2-Methylacetoacetyl-CoA thiolase deficiency	2-Methylacetoacetyl-CoA thiolase	—	Poss CC
(v) Disorders of the γ-glutamyl cycle			
5-Oxoprolinuria	Glutathione synthetase	—	Poss CC
γ-Glutamylcysteine synthetase deficiency	γ-Glutamylcysteine synthetase	—	Poss CC
γ-Glutamylcysteine synthetase deficiency	γ-Glutamyltranspeptidase	—	Poss CC
5-Oxoprolinase deficiency	5-Oxoprolinase	—	Poss CC
(vi) Other organic acid disorders			
Alkaptonuria	Homogentisic acid oxidase	—	UNK
Glutaric aciduria type I	Glutaryl-CoA dehydrogenase	—	AF, CVB
Glutaric aciduria type II	Electron transfer flavoprotein (ETF) ETF:ubiquinone oxidoreductase	—	AF, CVB
Glycerol kinase deficiency	Glycerol kinase	Xp21·3–p21·2	AF, CVB
Hyperoxaluria type I (glycolic aciduria)	Alanine:glyoxylate aminotransferase	—	FT
Hyperoxaluria type II (glyceric aciduria)	Glyceric dehydrogenase	—	UNK
Canavan's disease	Aspartoacylase	—	Poss MET
(E) FATTY ACID OXIDATION DEFECTS			
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	Short chain acyl-CoA dehydrogenase	12q22-qter	Poss CC
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)	Medium chain acyl-CoA dehydrogenase	1p31	DNA/CVB
Long chain acyl-CoA dehydrogenase deficiency (LCAD)	Long chain acyl-CoA dehydrogenase	7	Poss CC
(F) LYSOSOMAL ENZYME DEFECTS			
(i) Mucopolysaccharidoses			
Type IH (Hurler's syndrome)	Iduronidase	4p16·3	AF, CVB
Type IS (Scheie's syndrome)	Iduronidase		
Type II (Hunter's syndrome)	Iduronate sulphatase	Xq28	AF, CVB
Type III (Sanfilippo's syndrome)			
A	Heparan N-sulphatase	—	AF, CVB
B	N-acetylglucosaminidase	—	AF, CVB
C	Acetyl-CoA-glucosaminide acetyltransferase	—	AF, CVB
D	N-acetylglucosamine 6-sulphatase	12q14	Poss CC
Type IV (Morquio's syndrome)			
A	Galactosamine 6-sulphatase	—	
B	β-Galactosidase	3p21-cen	Poss CC
Type VI (Maroteaux-Lamy syndrome)	N-acetylgalactosamine 4-sulphatase	5q11-q13	AF, CVB
Type VII (Sly's disease)	β-Glucuronidase	7q11·2–q22	Poss CC

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(ii) Mucolipidoses			
Mucolipidosis II (I-Cell disease)	UDP-N-acetylglycosamine: lysosomal enzyme N-acetylglucosaminyl-1-phosphotransferase	—	AF, CVB
Mucolipidosis III (pseudo-Hurler polydystrophy)	Same as mucolipidosis II	—	AF, CVB
(iii) Glycoproteinoses			
α-Mannosidosis	α-Mannosidase	19p13·2–q12	AF, CVB
β-Mannosidosis	β-Mannosidase	—	Poss CC
Fucosidosis	α-Fucosidase	1p34	AF, CVB
Aspartylglycosaminuria	Aspartylglycosaminidase	4q21-qter	AF, CVB
Sialidosis type I (cherry-red spot-myoclonus syndrome)	Neuraminidase	6p21·3	AF, CVB
Sialidosis type II:			
Congenital and infantile	Neuraminidase	6p21·3	AF, CVB
Juvenile	Combined neuraminidase and β galactosidase deficiency	20	AF, CVB
(iv) Gm_2 gangliosidoses			
Tay-Sach's disease (variant B)	Hexosaminidase α-subunit	15q22–q25·1	AF, CVB
Sandhoff's disease (variant 0)	Hexosaminidase β-subunit	5q13	AF, CVB
Gm_2 activator deficiency (variant AB)	Gm_2 activator protein	5	Poss CC
(v) Other lysosomal storage disorders			
Metachromatic leucodystrophy	Arylsulphatase A	22q13	AF, CVB
Multiple sulphatase deficiency	Multiple lysosomal sulphatases	—	AF, CVB
Niemann-Pick disease:			
Type A	Sphingomyelinase	17	AF, CVB
Type B	Sphingomyelinase	17	AF, CVB
Type C	Cholesterol esterification		AF, CVB
Farbers	Ceramidase		AF, CVB
Gaucher's disease:			
Type 1 (non-neuronopathic)	Glucocerebrosidase	1q21	AF, CVB
Type 2 (acute neuronopathic)	Glucocerebrosidase	1q21	AF, CVB
Type 3 (Norrbottnian)	Glucocerebrosidase	1q21	AF, CVB
Krabbe's disease	Galactocerebrosidase	14	AF, CVB
Fabry's disease	α-Galactosidase	Xq22	AF, CVB
Schindler's disease	α-N-acetylgalactosaminidase	22q13–qter	Poss CC
Gm_1 gangliosidosis	β-Galactosidase	3p21–cen	AF, CVB
Wolman's disease	Acid lipase	10q	AF, CVB
Cholesterol ester storage disease	Acid lipase	10q	AF, CVB
Mucolipidosis type IV	?Ganglioside sialidase	—	HIST
(G) PEROXISOMAL DISORDERS			
Zellweger syndrome	Peroxisome biogenesis	7q11·23	AF, CVB
Neonatal adrenoleucodystrophy	Peroxisome biogenesis	—	AF, CVB
Infantile Refsum's syndrome	Peroxisome biogenesis	—	AF, CVB
(For disorders of peroxisome biogenesis a peroxisomal enzyme—dihydroxyacetone phosphate acyltransferase can be assayed)			
Rhizomelic chondrodysplasia punctata	Multiple peroxisomal enzymes	—	AF, CVB
Pseudo-Zellweger syndrome	3-Oxoacyl-coenzyme A thiolase	3p23–p22	AF, CVB
Pseudo-neonatal adrenoleucodystrophy	Acyl-CoA oxidase	—	Poss CC
X linked adrenoleucodystrophy	Very long chain fatty acid ligase	Xq28	AF, CVB
Refsum's disease	Phytanic acid hydroxylase	11p13	Poss CC
Acatalasia	Catalase	—	UNK
(H) PURINE AND PYRIMIDINE METABOLISM			
Lesch-Nyhan syndrome	Hypoxanthine phosphoribosyltransferase	Xq26-q27	AF, CVB
Adenine phosphoribosyltransferase deficiency	Adenine phosphoribosyltransferase	16q	AF, CVB
Adenosine deaminase deficiency	Adenosine deaminase	20q13·1	AF, CVB
Purine nucleoside phosphorylase deficiency	Purine nucleoside phosphorylase	14q13	AF, CVB

Condition	**Enzyme deficiency**	**Chromosome location**	**Prenatal diagnosis**
Myoadenylate deaminase deficiency	Myoadenylate deaminase	—	AF, CVB
Xanthinuria	Xanthine oxidase	—	UNK
Orotic aciduria	Uridine-5′-monophosphate synthase	3q13	Poss CC
Pyrimidine-5′-nucleotidase deficiency	Pyrimidine-5′-nucleotidase	—	UNK
(I) TRACE METAL METABOLISM			
Wilson's disease	Basic defect unknown	13q14	Poss DNA
Menke's disease	Basic defect unknown	Xq13	AF, CVB
Haemachromatosis	Basic defect unknown	6p21·3	UNK
Molybdenum cofactor deficiency	Molybdenum cofactor	—	AF, CVB
Isolated sulphite oxidase deficiency	Sulphite oxidase	—	Poss CC
(J) LIPID METABOLISM			
Abetalipoproteinaemia	Abnormal handling of apolipoprotein B	2p24	UNK
Lipoprotein lipase deficiency	Lipoprotein lipase	8p22	UNK
Lecithin:cholesterol acyltransferase deficiency (LCAT)	Lecithin:cholesterol acyltransferase	16q	UNK
Familial hypercholesterolaemia (hyperlipidaemia type IIA)	Deficient low density lipoprotein (LDL) receptors	19p13·1–13·3	AF
Dysbetalipoproteinaemia (type III, hyperlipidaemia)	Defective apolipoprotein E	19	UNK
Tangier disease	Defective high density lipoprotein (HDL) metabolism	—	UNK
Cerebrotendinous xanthomatosis	Mitochondrial 26-hydroxylase	—	UNK
Phytosterolaemia	Basic defect unknown	—	UNK
(K) VITAMIN METABOLISM			
(i) Folic acid			
Methylene tetrahydrofolate reductase deficiency	Methylene tetrahydrofolate reductase	—	AF, CVB
Glutamate formiminotransferase deficiency	Glutamate formininotransferase	—	No
(ii) Vitamin B_{12} (cobalamin)			
Transcobalamin II deficiency	Transcobalamin II	22q11·2qter	Poss CC
Defects in adenosylcobalamin (AdoCbl) synthesis:			
cbl A mutation	Basic defect unknown	—	AF, CVB
cbl B mutation	ATP:cob(I)alamin adenosyltransferase	—	AF, CVB
Both defects cause methylmalonic acidaemia as AdoCbl is an essential cofactor for the mutase enzyme			
Defects in methylocobalamin (MeCbl) synthesis:			
cbl E mutation	Basic defect unknown	—	AF
cbl G mutation	Basic defect unknown	—	Poss CC
Both disorders lead to a functional deficiency of N^5-methyltetrahydrofolate:homocysteine methyltransferase leading to homocystinuria, hypomethioninaemia without methylmalonic acidaemia			
cbl C mutation	Basic defect unknown	—	Poss CC
cbl D mutation	Basic defect unknown	—	Poss CC
cbl F mutation	Cobalamin transport from lysosome	—	Poss CC
(L) DEFECTS IN THE SYNTHESIS AND DEGRADATION OF HAEM PROTEINS			
(i) Porphyrias			
δ-Aminolevulinic acid dehydratase deficiency	δ-Aminolevulinic acid dehydratase	9q34	UNK
Acute intermittent porphyria	Porphobilinogen deaminase	11q23–qter	AF
Congenital erythropoietic porphyria	Uroporphyrinogen III cosynthase	—	MET
Porphyria cutanea tarda	Uroporphyrindecarboxylase	1qter–p21	No
Hereditary coproporphyria	Coproporphyrinogen oxidase	9	Poss CC
Variegate porphyria	Protoporphyrinogen oxidase	14q32	Poss CC
Erythropoietic protoporphyria	Ferrochelatase	—	Poss CC

Condition	**Enzyme deficiency**	**Chromosome location**	**Prenatal diagnosis**
(ii) Bilirubin metabolism			
Crigler-Najjar syndrome type I	UDP-glucuronyltransferase	—	No
Crigler-Najjar syndrome type II	UDP-glucuronyltransferase	—	No
Gilbert's syndrome	UDP-glucuronyltransferase	—	No
Dubin-Johnson syndrome	Basic defect unknown	—	No
Rotor syndrome	Basic defect unknown	—	No
(M) DISORDERS OF MEMBRANE TRANSPORT			
Cystinuria	Renal and intestinal transport defect	—	No
Lysinuric protein intolerance	Defect of cationic amino acid transport	—	No
Hartnup disease	Defect of neutral amino acid transport	—	No
Cystinosis	Lysosomal cystine transport	—	AF, CVB
Infantile free sialic acid storage disease	Lysosomal sialic acid transport	—	AF, CVB
Salla disease	Lysosomal sialic acid transport	—	AF
(N) MISCELLANEOUS DISORDERS			
Lowe's syndrome	Basic defect unknown	Xq25	UNK
Carbonic anhydrase II deficiency	Carbonic anhydrase II	8q22	No
Steroid sulphatase deficiency	Steroid sulphatase	Xpter–p22·32	AF, CVB
Hypophosphatasia	Alkaline phosphatase	1p	AF
Fumaric aciduria	Fumarase	—	Poss CC
Sjögren-Larsson syndrome	Fatty alcohol NAD oxidoreductase	—	Poss CC

AF: cell free amniotic fluid or cultured amniocytes. *CVB:* assay performed on either uncultured or cultured villus cells. *Poss CC:* as far as authors' are aware prenatal diagnosis has not been performed for these disorders. However, enzyme is expressed in fibroblast cells and theoretically could be used as the basis of a prenatal test. *Poss DNA:* the genetic mutation causing these disorders has been established and may be the most appropriate approach to prenatal testing. *Poss FT:* the enzyme deficiency can only be detected in fetal tissue. This would usually require a fetal liver biopsy, but in some instances direct fetal blood sampling by cordocentesis. *MET:* metabolites from fetal urine are detected in samples obtained by amniocentesis at 14–16 weeks' gestation. *UNK:* as far as the authors' are aware prenatal diagnosis has not been attempted. In a number of cases the exact biochemical defect is yet to be established. ***: assay of the total activity of the pyruvate dehydrogenase complex is possible, but as far as the authors' are aware has not been applied to prenatal testing. Partial deficiencies are common leading to difficulty in interpreting results. *###:* only one component of the respiratory transport chain (complex IV, cytochrome oxidase) has been studied prenatally. In families with a deletion of mitochondrial DNA a molecular approach may be more appropriate. *HIST:* histological changes (usually abnormal lysosomal inclusions) within amniocytes have been used as a prenatal test. UDP: uridine diphosphate.

Archives of Disease in Childhood 1991; **66:** 823–826

CURRENT TOPIC

Computerised neonatal information systems

S A Spencer

North Staffordshire
Maternity Hospital,
Hilton Road,
Harpfields,
Stoke on Trent ST4 6SD

Correspondence to:
Dr Spencer
from whom the *Bibliography* is available (please send a stamped, addressed envelope).

Since its inception the British Paediatric Association (BPA) computer group has provided a forum for the demonstration of neonatal information systems. Of the 10 reported at BPA meetings from 1984–90 eight are currently still in use.[A-J] One of the first systems to be presented was developed primarily to assist with neonatal audit.[1] Now that participation in audit is a requirement for all doctors the interest in computerised information systems has increased and is no longer confined to a small group of enthusiastic pioneers. Detailed information about workload and outcome will soon be required for the purpose of negotiating contracts between purchasers and providers and it is difficult to see how this can be acheived without access to database technology. Many of the systems demonstrated have been highly successful and a number have been implemented in more than one unit. The guidance given below has been formulated after discussion with those involved in developing these systems.

The dataset

The key to any information system is to formulate an appropriate dataset. This should include the categories shown in table 1. With the power of modern database technology there is a tendency to collect a great deal more data than one could ever possibly use. This leads to a very cumbersome system and much frustration on the part of those who collect or input data but never see it used. Therefore it is most important to base the dataset on planned outputs of the type illustrated in table 2. In this way the dataset will be precise and relevant and those using the computer will be able to appreciate the value of the data they collect. This will greatly enhance the quality of data collection.

Table 1 Guide to neonatal dataset

Categories	*Examples of information collected*
Demographic	Name Address Hospital number
Mother	Medical history Family history Past obstetric history Antenatal history Delivery
Admission details	Date and time Origin Reason
Progress	Diagnoses Procedures Medication Feeding
Discharge details	Date and time Destination Outcome Follow up arrangements
Recommendations	Discharge medication Immunisation

Table 2 Type and purpose of output

Type of output	*Purpose of output*
Front sheet summary of mothers	For easy reference to important information at the front of the child's neonatal record
Comprehensive discharge summary	Communicate with general practitioner Permanent record
ICD9 coded diagnoses	Körner requirements
Regular cumulative reports on: Perinatal mortality Admissions and survival Mortality review Outcome for tranfers Intracranial scan results Ventilation review Procedure review Infection and antibiotics Workload	Comprehensive annual report Audit Resource management Quality assurance Research

The pioneer systems are very individualisitic with respect to the dataset. Even when similar information is collected there may be variations in the coding classifications used. For example, in one system all attempted umbilical artery catheterisations may be recorded, another may record only successful catheterisations. A third may not distinguish between umbilical and radial artery catheterisation. Such differences mean that it will be difficult to compare data collected on different databases. For this reason it would be helpful if an interested group formulated an agreed core dataset which should not be large but should be carefully defined. Each unit could then add its own embellishments to cater for local information requirements which vary greatly from one unit to another.

Diagnostic coding

There is a need for diagnostic coding both for Körner requirements and so that patients with like conditions can easily be compared. Unfortunately the *International Classification of Diseases, 9th revision* (ICD9) codes are inadequate for neonatal use for a number of reasons. First, there is often inadequate detail. The ICD9 code for Menkes's syndrome and Zellweger's syndrome is not different. Second, the diagnostic label attached to the code may vary from local usage. Few of our senior house officers refer to umbilical cord sepsis as omphalitis. Third, certain important conditions require coding in two parts. Listeria pneumonia is coded as 'pneumonia bacteria (NOS)' and 'listeriosis infection'. Fourth, when coding for a unilateral lesion it is not possible to code for the side of the lesion. Finally, only a small subset of the ICD9 coding system is relevant to neonatology. In the North Staffordshire Maternity Hospital over a one year period 460 babies were given 1322 coded diagnoses. Only 145 different codes were used, although 370 were available in the computer dictionary.

In order to overcome these difficulties a number of neonatal databases use their own dictionary of codes.[2] Most of these are cross referenced for ICD9 codes. With ICD9 an additional digit can be added to the existing codes to create more subgroups. As such dictionaries are not exhaustive a facility to add additional codes is required. It is also helpful if the user can enter diagnoses in free text when an appropriate coded diagnosis is not available. These can be coded later when the dictionary has been amended.

A comprehensive dictionary of codes specific for neonatal diagnoses that could be utilised by all would be a great asset. Documentation should include definitions of some of the more controversial diagnostic categories so as to ensure uniformity in the coding of conditions such as bronchopulmonary dysplasia, transient tachypnoea, birth asphyxia, and necrotising enterocolitis. Such a dictionary of codes is under development and may be available shortly (the BPA Diagnostic Codes Project).

Obtaining an accurate and complete list of diagnostic codes for each patient is not a trivial problem. This can be achieved only by involving medical staff in the coding process. It is helpful if guidance is provided by senior doctors on a regular basis, either on ward rounds or at regular coding meetings.[C] Diagnoses appropriate to each patient can be selected from the dictionary that may be available on line, although it can be easier to refer to a printed copy.

Powerful diagnostic support software based on the Read system is now available to assist with the task of coding. When a unique diagnosis such as 'Down's syndrome' is entered this is immediately accepted and automatically coded. A partial diagnosis such as 'pneumonia' will give rise to a comprehensive list of diagnoses that include pneumonia. These are normally presented in a window on the screen. The coder is thereby encouraged to consider making a more precise diagnosis, although the option of making a non-specific diagnosis will remain. This type of coding support encourages diagnostic accuracy, saves time, and is fun to use.

In neonatology it is common for a number of codable diagnoses such as pneumothorax or intraventricular haemorrhage to be included in the dataset. It is easy for these to be forgotten unless they are automatically coded and included in any list of diagnoses generated for the patient.

Data input

The simplest method of data input is to provide a worksheet that is completed during the patient's stay.[3] There may be different sections of the work sheet for clerical, nursing, and medical staff. When the worksheet is complete clerical staff may enter the data into the computer or an optical reader can be used to avoid transcription errors.[F] The main disadvantage of this method is that there is no interaction between the computer and user. Such interaction can be used to improve the quality of data collected as exemplified by the coding support software described above. Furthermore if a large amount of data is collected then a questionnaire based system becomes cumbersome.

When doctors and nurses are required to enter data as part of their daily routine it is most important that the database is easy and quick to use. One source of frustration for busy staff is a slow response time. A requirement to answer numerous irrelevant questions is another. The latter may be avoided by using key items to determine which parts of the dataset are relevant to the individual patient and selecting only these for completion.[J 4]

Data may be collected in real time or retrospectively. In a clinic with a terminal on the desk there is no doubt that real time data collection is the ideal method. This is not necessarily true of neonatal data collection. To collect all of this data in real time would require access to a terminal from each cotside. Furthermore preterm infants change condition rapidly and this can lead to the collection of superfluous data. For example, a child may have a number of different cranial ultrasound scan appearances before developing right periventricular leukomalacia. Clearly those with a special interest in cranial ultrasonography will wish to record all the changes observed, but in most situations a final summary diagnosis will be more useful and easier to analyse later.

Information collection should be tailored to fit in with the working practices of the unit. It is often very helpful to record details of admissions and discharges in real time so that the computer can be used to keep track of the patients. Some information may usefully be recorded on a daily basis. This might include blood culture results, the use of intermittent positive pressure ventilation, and nursing dependency levels. In this way a running total of ventilation days and other similar parameters can be made available. Finally at the point of discharge or shortly afterwards other information including diagnosis codes may be added retrospectively.

Demographic data may be entered by clerks. Nurses are often in the best position to review progress on a daily basis and enter this type of data. For the reasons outlined above diagnostic information is probably best entered by medical staff. This task is made considerably easier if a problem list is kept at the front of the notes.

Data audit

It is very difficult to assess the quality of information stored in hospital notes and the fact that vital information is missing may not come to light until it is required at some time in the future. In contrast computerised data fields can and should be checked on a regular basis. Programs can be written to search data fields and produce an analysis indicating which data items are missing in which patients. In this way data collection can be audited. When the users are required to input the missing data the quality of initial data collection rapidly improves.

When admissions and discharges are recorded in real time it is possible to use the computer to highlight patients who have not had the dataset completed and diagnostic codes added. In this way it is possible to get quality information on 100% of patients for later analysis.

Output requirements

It is imperative that those who have the task of entering data are rewarded with a useful output.[5] For example at the North Staffordshire Maternity Hospital it had been a nursing task to copy details from the maternity notes onto a form that was then filed in the front of the neonatal notes. This task was replaced by the task of entering similar information into the database. On completion a front sheet summary was printed, checked for errors, and filed in the front of the notes. The summary proved to be of value to the medical team when reviewing the case. A similar principle applies to the production of a computerised discharge summary that may obviate the need for a dictated summary.

Computerised discharge summaries are often criticised for being impersonal and less informative than dictated summaries. On the other hand they are less likely to have important items of information missing and they tend to be available earlier and in a higher proportion of patients.[6,7] In our experience an enormous amount of secretarial time can also be saved. The personal touch can be added by including comments in free text, although there is a tendency for junior doctors to concentrate on the dataset and ignore this facility. The format of the letter will make a lot of difference to its readibility and usefulness and therefore it is well worth investing time and effort to get this right.

The prime objective in setting up a neonatal database is to be able to use the data collected. Certain information will be required on a regular basis (table 2) and it is well worth generating such information as a standard report that can be produced for any time period at the touch of a button. As an example the quality parameters required by the West Midlands Regional Health Authority for monitoring regionally funded neonatal intensive care are shown in table 3. It seems likely that similar information will be required by other purchasers of neonatal services.

Standard reports will not cater for unforeseen or one off information requirements and so it is very useful to be able to conduct an ad hoc inquiry. This normally consists of a list of patients with characteristics that have been specified from the dataset by the inquirer. Once the selection has been made it is normally possible to stipulate which information is to be printed out in the selected patients. Facilities to sort patients may also be available. Databases vary in the complexity and ease of use of their inquiry language but ideally it should be possible for someone with little or no programming experience to obtain information in this way.[8]

Table 3 Quality parameters for neonatal intensive care

Quality parameter	*Stratification*
Admissions	Birth weight, gestation, inborn/ outborn/in utero transfer
Mortality	Birth weight, gestation, early/late deaths
Ventilation:	
Duration	Birth weight, gestation
Outcome	Birth weight, gestation
Air leaks	Birth weight, gestation
Bronchopulmonary dysplasia	
Necrotising enterocolitis	Birth weight, gestation
Retinopathy >grade 3	Birth weight, gestation
Cranial ultrasound scan	Birth weight, gestation
Postmortem examination	Birth weight, gestation

Interface with other systems

Demographic information must be available for effective data analysis. This is recorded in many hospitals on a patient administration system. Clearly it is useful if the neonatal database can be linked for electronic transer of such details. Neonatal and maternity records have much data in common and therefore when both are to be computerised, communication or complete integration is desirable.[E J] This will obviate the need for laborious transcription of antenatal records. Ideally the delivery record and neonatal record should form the basis of the paediatric record. A link with the community child health computer is also desirable. Although laboratory links are useful for obtaining clearly tabulated results, this is less essential for acute neonatal management than for the long term management of children in outpatient clinics.

Many district health authorities are making plans for the development of hospital wide integrated information systems and therefore it is important to consider how any proposed neonatal database will interface into such a system. Almost certainly the district information system will require coded diagnoses and other Körner data. Consideration also needs to be given to the possibility of transferring data electronically into other software packages. These may be used for word processing, statistical analysis, or graphical presentation.

Software considerations

Some of the earlier neonatal databases were written from scratch usually by an enthusiastic doctor and a programming expert.[A] Although this approach has been successful, it is much easier to start with a database program which can be configured to meet ones own requirements.[H] Several of the aforementioned systems have been developed in this way. At first sight it may seem easy to develop a new neonatal application using such a database program, but the considerable time and effort required to get a system operational should not be underestimated. Therefore it is better to adopt and adapt a system that has already been developed rather than starting again. Probably the only good reason for writing a new neonatal application is in cases where the district adopts a database package that does not have a neonatal module and there is commercial support for the development of such.

System support

In choosing or writing a database application, consideration must be given to the support of the system. There is considerable variation in database size and complexity. A system resident on a single microcomputer with a relatively small dataset and no interface with other systems will require much less support than a large multiuser system interfacing with other hospital information systems and keeping data on line for many years. Although single user systems have proved very valuable the large multiuser systems are much more likely to be able to adapt and grow to meet new challenges as district information systems continue to develop. Support for such systems will need to be provided in a number of ways. Technical support will be required for both hardware and software. It is a disaster if a system goes down for days or weeks once it has been integrated into a department. It is almost impossible to catch up with the data backlog in such an eventuality.

Continued software development is essential. Once a system is operational deficiencies inevitably become apparent. Furthermore working practices and information needs change with time. Modification of the dataset or data analysis program may be a problem if system support is dependent on one individual who may leave the project after implementation. Some applications are commerically supported, which can be very useful provided the cost of modification is not prohibitive. Systems that cannot be modified are likely to atrophy and eventually die.

Training support is a requirement that is often forgotten. It is essential that all grades and types of users are taught how to use the system. Many junior doctors still have no computing training and therefore may require a lot of support when first introduced to a system. With rapid staff turnover this is an ongoing requirement. Finally a comprehensive manual is an asset.

1 Williams THC, Davies DP. Medical audit in neonatal care. *BMJ* 1980;**281**:1618–20.
2 Christo GG, Shenoy S, Amin S, Marianus BVP, Baliga M, Venkatesh A. A computerised neonatal database and automated discharge summaries. *Indian Pediatrics* 1987;**24**: 1105–9.
3 Nagey DA, Wright JN, Mulligan K, Crenshaw C. A convertible perinatal database. *M D Comput* 1989;**6**:28–36.
4 Lissauer T, Dawson AM, Beard RW. Computerised information system for neonatal intensive and special care. *J Perinat Med* 1987;**15**(suppl 1):64.
5 Ellis J, Shipham S, Moloantoa C, Monja P. Computerized matron's report. The basis of a neonatal information system. *Curations* 1987;**10**:22–23.
6 Lissauer T, Paterson CM, Simons A, Beard RW. Evaluation of computer generated neonatal discharge summaries. *Arch Dis Child* 1991;**66**:433–6.
7 Sultan S, Caangay D, Williams L, Rodgers K. Use of personal computer to create data base and generate discharge summary in private practice in neonatology. *J Perinat Med* 1987;**15**(suppl 1):63.
8 Gallagher A. Neonatal information system. *J Perinat Med* 1987;**15**(suppl 1):245.

Bibliography
A Skeffington FS, Simmonds DAD, O'Neill EM. Computerised neonatal in-patient clinical records. *BPA Abstract* 1984;**P58**:48.
B Smith MJ, Edmond ED, Cooke RWI. Micro-computer generated discharge summary for a regional neonatal intensive care unit. *BPA Abstract* 1984;**P59**:48.
C Williams THC, Woods JR, Davies DP. Neonatal audit—an ongoing system. *BPA Abstract* 1984;**P60**:48.
D Meerstadt PWD. A simple neonatal micro-computer database. *BPA Abstract* 1984;**P63**:49.
E Maresh M, Dawson AM, Beard RW, Rivers RPA, Lissauer T. Perinatal microcomputer information system. *BPA Abstract* 1985;**P55**:55.
F Chan MCK, Moody JB, Silver H, Davidson DC. Neonatal records—data capture using optical mark reader (OMR) forms. *BPA Abstract* 1985;**P57**:55.
G Mohammed T, Robinson MJ. Computer assisted neonatal database and discharge summary. *BPA Abstract* 1986;**P48**: 53.
H Ross Russell RI, Hamilton PA. A neonatal database using Smart$^{\text{TM}}$: home grown advantages. *BPA Abstract* 1989; **G7**:P43.
I Lyon AJ, Morgan-Jones D. Audit in the neonatal unit—the development of a computer database. *BPA Abstract* 1990; **G11**:45.
J Spencer SA. Neonatal data analysis using the north Staffordshire neonatal database. *BPA Abstract* 1990;**G12**:45.

Archives of Disease in Childhood 1991; **66:** 827–828

PERINATAL LESSONS FROM THE PAST

Dr Langdon Down (1828–1896) and 'mongolism'

P M Dunn

University of Bristol, Southmead Hospital

Correspondence to:
Professor P M Dunn,
Department of Child Health,
Southmead Hospital,
Southmead Road,
Bristol BS10 5NB.

John Langdon Down was born at Torpoint in Cornwall in 1828. After local schooling he became apprenticed at the age of 14 for four years to his father, a local apothecary. Then, wishing to become a scientist, in 1846 he entered a laboratory of the Pharmaceutical Society in London. There he won a prize for organic chemistry and also came into contact with Michael Faraday. In 1853 his father died and he decided to take up medicine, entering the London Hospital at the age of 25 and qualifying five years later with many honours and prizes including the gold medal for physiology. In 1858 he was appointed Medical Superintendent of the Earlswood Asylum for Idiots at Redhill in Surrey, a position he retained for 10 years before establishing his own institution for mentally retarded children, Normansfield, at Teddington. Within a year of qualifying he had obtained both the MRCP and MD, and had been elected to the staff of the London Hospital as a physician. There he taught therapeutics and medicine, and his humanity and care for the mentally retarded brought him a large private practice. Down did not write a great deal but is eponymously remembered for his classic description of mongolism in a short essay in 1866,[1] from which the following extracts are taken:

'The medical practitioner who may be consulted in any given case, has, perhaps in a very early condition of the child's life, to give an opinion on points of vital importance as to the present condition and probable future of the little one. Moreover, he may be pressed as to the question, whether the supposed defect dates from any cause subsequent to the birth or not. Has the nurse dosed the child with opium? Has the little one met with any accident? Has the instrumental interference which maternal safety demanded, been the cause of what seems to the anxious parents, a vacant future? Can it be that when away from the family attendant the calomel powders were judiciously prescribed? Can, in fact, the strange anomalies which the child presents, be attributed to the numerous causes which maternal solicitude conjures to the imagination, in order to account for a condition, for which any cause is sought, rather than hereditary taint or parental influence.

I have for some time had my attention directed to the possibility of making a classification of ~~the feeble-minded, by arranging them around~~ various ethnic standards . . .'

Dr John Langdon Down (1828–96).

'The great Mongolian family has numerous representatives, and it is to this division, I wish, in this paper, to call special attention. A very large number of congenital idiots are typical Mongols. So marked is this, that when placed side by side, it is difficult to believe that the specimens compared are not children of the same parents. The number of idiots who arrange themselves around the Mongolian type is so great, and they present such a close resemblance to one another in mental power, that I shall describe an idiot member of this racial division, selected ~~from the large number that have fallen~~ under my observation.

The hair is not black, as in the real Mongol, but of a brownish colour, straight and scanty. The face is flat and broad, and destitute of prominence. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another. The ~~palpebral fissure~~ is very narrow. The forehead is wrinkled transversely from the constant assistance which the ~~levatores palpebrarum derive from the occipito-~~frontalis muscle in the opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick, and is much roughened. The nose is small. The skin has a slight [redacted]

tions that the differences in the races are not specific but variable.

These examples of the results of degeneracy

Calculate with confidence

CIA software

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton. The program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- non-parametric analyses

For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program may also be used in conjunction with the book *Statistics with Confidence,* which provides numerous worked examples. The software is available for IBM compatibles on either a 5¼″ or a 3½″ disk.

[redacted]

[redacted]

JULY 1991 VOL 66 NO 7

Acc 92

[illegible]

ARCHIVES OF DISEASE IN CHILDHOOD

[redacted]

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Editors: Bernard Valman, Malcolm Chiswick
Associate Editors: Derek Johnston, Michael Silverman, Brian Wharton
Statistical Adviser: Michael Healy
Technical Editor: Sue Heels
Editorial Assistant: Jacinta Marshall

EDITORIAL COMMITTEE

F Cockburn
T J David
M J Dillon
M E Garralda
H L Halliday
I M Hann
I A Hughes
J W Keeling
C R Kennedy
S W Lenton
J K Lloyd
H Marcovitch
N McIntosh
P J Milla
L Polnay
P Raine
P T Rudd
J F N Taylor
R M Winter
J E Wraith
Editor, *BMJ*

NOTES TO CONTRIBUTORS Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

NOTICE TO ADVERTISERS Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

NOTICE TO SUBSCRIBERS *Archives of Disease in Childhood* is published monthly. The annual subscription rates are £127 inland and £140 overseas (USA $208). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All inquiries however must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All inquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

The British Paediatric Association is a registered charity.

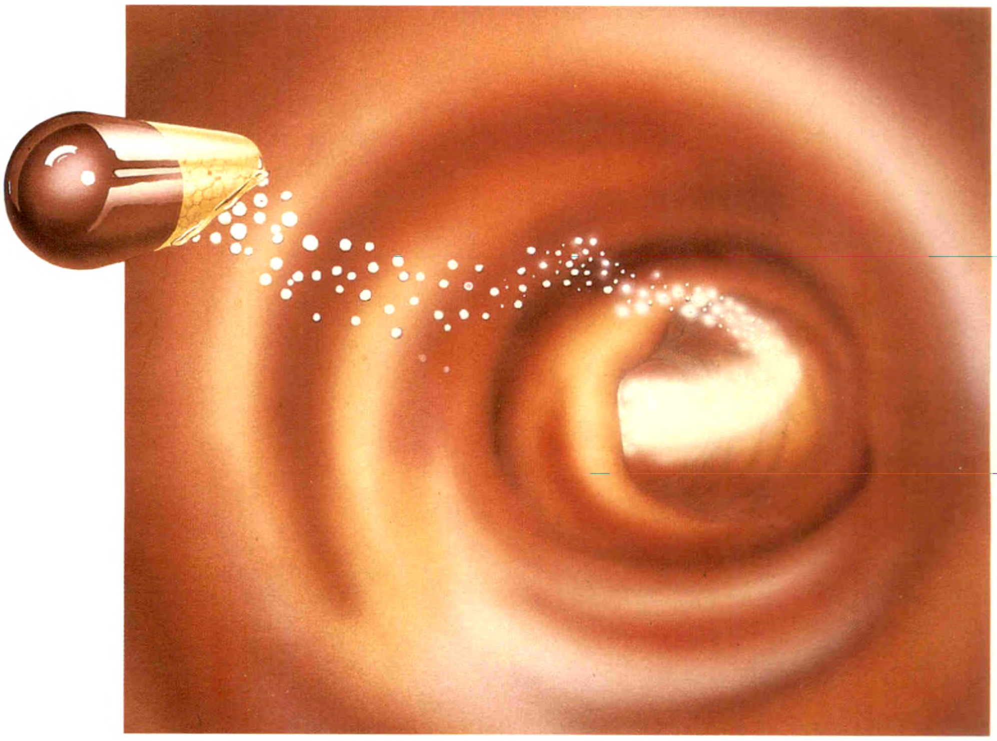
COPYRIGHT © 1991 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Published by the British Medical Association, Tavistock Square, London WC1H 9JR and printed in England by The Devonshire Press Ltd, Torquay.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0003-9888

PROGRESS
In The Management Of Cystic Fibrosis



creon®
pancreatin

RIGHT ON TARGET – RIGHT FROM THE START

Prescribing Information – Presentation: Brown-yellow capsules containing enteric coated granules of pancreatin equivalent to: 9,000 BP units of amylase, 8,000 BP units of lipase, 210 BP units of protease. Available in packs of 100. Basic NHS price £13.33. **Indication:** Pancreatic exocrine insufficiency. **Dosage and administration:** Adults and children: Initially one or two capsules with meals, then adjust according to response. The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with fluid or soft food, but without chewing. If the granules are mixed with food, it is important that they are taken immediately, otherwise dissolution of the enteric coating may result.

Contra-indications, Warnings, etc: Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis. Warnings: Use in pregnancy: There is inadequate evidence of safety in use during pregnancy. The product is of porcine origin. Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported with high doses of pancreatin. Overdosage could precipitate meconium ileus equivalent. Perianal irritation could occur, and, rarely, inflammation when large doses are used. **Product Licence Number:** 5727/0001. **Name and address of Licence Holder:** *Kali Chemie Pharma GmbH* Postfach 220, D-3000, Hannover 1, West Germany.

duphar Further information is available from:
Duphar Laboratories Limited, Gaters Hill, West End, Southampton SO3 3JD. Tel: 0703 472281.

CRAd/PEI/1/8

UNIVERSITY COLLEGE LIBRARY

Making sure Ventolin gets through to the younger generation
VENTODISKS
8
1
2
3
4
5
6
7
A
H

VENTODISKS

(Salbutamol BP)

odisks (Salbutamol BP). **Abridged Prescribing Information** (Please refer to full data
t before prescribing.) **Uses**: Treatment and prophylaxis of acute and chronic broncho-
m. **Dosage and administration**: *Adults:* 400 micrograms as single dose or three
ur times daily. *Children:* 200 micrograms as single dose or three to four times daily.
tra-indications: Threatened abortion during first or second trimester. Hypersensitivity.
autions: If previously effective dose lasts less than three hours, seek medical advice.
ion in patients with thyrotoxicosis. Avoid use with non-selective beta-blockers.
okalaemia may occur, particularly in acute severe asthma. It may be potentiated by
hine derivatives, steroids, diuretics and hypoxia. Serum potassium levels should be
itored in such situations. *Pregnancy:* Avoid unnecessary use during early pregnancy.
consider if expected benefit outweighs possible risks. *Lactation:* Salbutamol likely to
be secreted in breast milk. Effect on neonate unknown. Balance risks against benefits.
Side effects: Mild tremor, headache occur rarely. Very rarely — transient muscle cram
hypersensitivity reactions. Potentially serious hypokalaemia may result from β_2-agonist
therapy. Paradoxical bronchospasm could occur – substitute alternative therapy.
Presentation and Basic NHS cost: Pack of 14 Ventodisks each containing 8 x 200
micrograms Salbutamol BP (as sulphate) — light blue or 8 x 400 micrograms Salbuta
(as sulphate) — dark blue, together with a Ventolin Diskhaler. For inhalation. £7·11 an
£12·02. Refill pack of 14 x 8 Ventodisks only. 200 micrograms, £6·54; 400 microgr
£11·45.
Product licence numbers: Ventodisks 200 micrograms 0045/0134, Ventodisks 40
micrograms 0045/0135.

ALLEN & HANBURYS

Further information is available on request from: Allen & Hanburys Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT
Ventodisks should only be used with a Ventolin Diskhaler. Diskhaler, Ventodisks and Ventolin are trade marks

Acc 12 7/93

ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Cleft lip—is there light at the end of the tunnel?

Cleft lip, with or without cleft palate (CL/P), is one of the commonest serious craniofacial malformations with an incidence of between one in 700 and one in 1000 live births. There can be little doubt about the impact the birth of an affected child has on a family. Problems with bonding and feeding are usually overcome with appropriate support and advice. Several operations may be needed throughout the growing years, as well as long term follow up by a team of specialists: plastic surgeons, orthodontists, ear, nose, and throat surgeons, speech therapists, dentists, and others. Despite advances in surgical and psychological management, there remains considerable confusion about the genetic implications of cleft lip. Is it a 'genetic' condition? Can parents be given an accurate risk of recurrence of this malformation? Current research looks set to answer, at least in part, some of these questions.

Family studies have shown that, after the birth of a child with isolated CL/P, the average recurrence risk for a couple with no family history of clefting is in the region of one in 25,[1] the figure varying with the severity of the cleft. The same figure applies for the child of a couple where one partner has CL/P. This 40-fold increase in risk over the general population suggests that some inherited element is important in the production of a cleft lip.

trait, albeit with incomplete penetrance and variable expression. It would seem that, in such families, a major gene is being passed from parent to child causing cleft lip. As it stands at present genetic counselling for CL/P is less than satisfactory, with couples being given an empirical recurrence risk after the birth of an affected child. If they then go on to have another affected child their risk increases further still as they have shown themselves to have a significant genetic predisposition. Identification of genetic loci that predispose to CL/P will help to distinguish these high risk from the low risk couples before an affected child is born.

A major tool of molecular genetics is linkage analysis, whereby potential candidate genes or genetic markers are studied in suitable pedigrees to see if they segregate with the condition more often than can be accounted for by chance. A number of studies of this type have already been completed and several markers have been excluded or shown to demonstrate weak linkage as a result.[5 6] Van der Woude's syndrome has been mapped to the long arm of chromosome 1,[7] and it would obviously be worth checking whether or not this marker shows linkage in other dominant CL/P families without lip pits.

Using genes which are likely, by their known function in

[redacted]

homologue of a gene known to cause a cleft like abnormality in the mouse.[11] Similarly, two unrelated cases of CL/P with translocation breakpoints at 10p13 have now been described, making this another area of potential study.[12]

The identification of a major locus is unlikely to be the end of the story. CL/P is almost certainly heterogeneous with other modifying genes playing some part in the development of a cleft. Also environmental factors, such as maternal phenytoin ingestion, are known to predispose to facial clefting, and it is possible that some continuous traits, such as face width, play a part.

The practical implication of the present research is the identification of individuals with a genetic predisposition to facial clefts. Prenatal diagnosis, with a view to termination of an affected fetus, tends not to be an issue in this condition, which is essentially amenable to surgical repair. Many couples do currently take up the option of a detailed ultrasound scan at about 18 weeks of pregnancy, as a non-invasive means of detecting the anomaly during pregnancy, and this allows them to prepare for the birth of an affected child.

S E HOLDER

Kennedy-Galton Centre,
Northwick Park Hospital,
Watford Road,
Harrow,
Middlesex HA1 3UJ

Dr Sue Holder is supported by the Medical Research Council. Thanks go to Dr RM Winter for his help with the preparation of the manuscript.

1 Harper PS. *Practical genetic counselling.* London: Wright, 1988:188–9.
2 Schinzel A. *Catalogue of unbalanced chromosome aberrations in man.* Berlin/New York: de Gruyter, 1983:850–1.
3 Gorlin RJ, Cohen MM Jr, Levin LS. *Syndromes of the head and neck.* New York/Oxford: Oxford University Press, 1990:698.
4 Fraser FC. Mapping the cleft-lip genes: the first fix? [Editorial.] *Am J Hum Genet* 1989;45:345–7.
5 Spence MA, Glass L, Crandall BF, *et al.* Genetic linkage studies with cleft lip and palate: report of two family studies. *J Craniofac Genet Dev Biol* 1983;3:207–12.
6 Eiberg H, Bixler D, Nielsen LS, Conneally PM, Mohr J. Suggestion of linkage of a major locus for nonsyndromic orofacial cleft with F13A and tentative assignment to chromosome 6. *Clin Genet* 1987;32:129–32.
7 Murray JC, Nishimura DY, Buetow KH, *et al.* Linkage of an autosomal dominant clefting syndrome (Van der Woude) to loci on chromosome 1q. *Am J Hum Genet* 1990;46:486–91.
8 Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC. Association of genetic variation of the transforming growth factor-alpha gene with cleft lip and palate. *Am J Hum Genet* 1989;45:348–53.
9 Fitzpatrick DR, Denhez F, Kondaiah P, Akhurst RJ. Differential expression of TGF beta isoforms in murine palatogenesis. *Development* 1990;**109**:585–95.
10 Kormann-Bortolotto MH, Farah LMS, Soares D, Corbani M, Muller R, Adell ACA. Terminal deletion 6p23: a case report. *Am J Med Genet* 1990;37:475–7.
11 Wakasugi S, Iwanaga T, Inomoto T, *et al.* An autosomal dominant mutation of facial development in a transgenic mouse. *Developmental Genetics* 1988;9:203–12.
12 Human Gene Mapping 10·5. *Cytogenet Cell Genet* 1990;55:335.

Adrenoleucodystrophy

There are few diseases more tragic than adrenoleucodystrophy (ALD). In a typical case a boy of between 5 and 9 years of age starts to have behavioural problems, difficulty with school work, becomes forgetful, and has problems finding his way about. He often appears to have difficulty in seeing, but is not obviously blind. He then starts to have further problems with memory and language. Within weeks or months the situation progresses so that he has some degree of unsteadiness, becomes incoordinated, and starts to fall. Still later on in the course of the disease his vision obviously becomes worse, and optic atrophy may be noted. He may become ataxic, dysarthric, and hemiparetic, and he starts to dement clearly. Seizures, often focal, are a late feature of the condition, but often within a year tragically the boy becomes bedridden and death usually ensues from intercurrent infections or complications of seizures within two to three years.

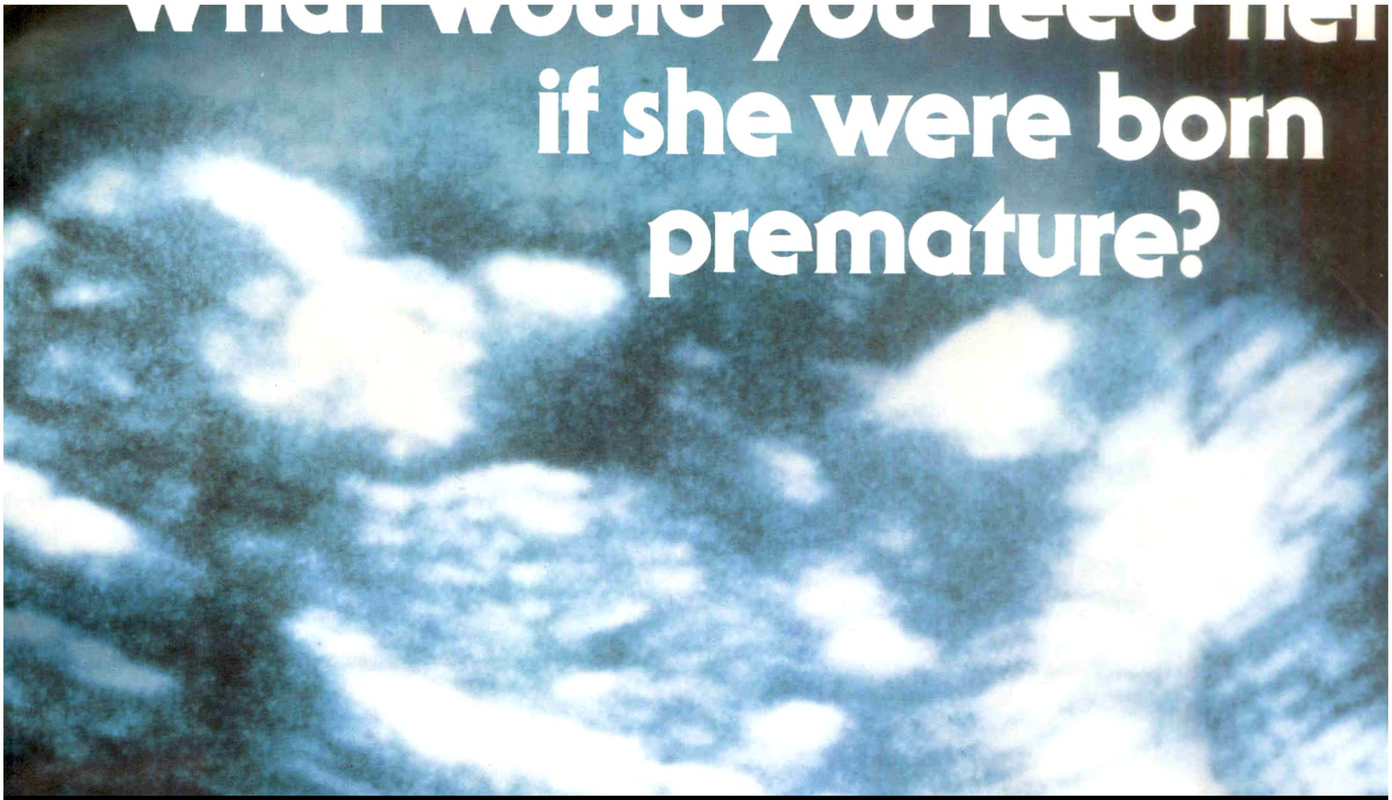
Although a number of early cases described as Schilder's disease[1] (encephalitis periaxalis diffusa) may have been cases of ALD, the first clear description of what we now know to be ALD was by Siemerling and Creutzfeldt.[2] Sometimes the name Addison-Schilder's disease has been applied in the past. Addison's name was added because occasionally these boys may develop dark skin pigmentation (melanoderma) associated with adrenal hypofunction and occasionally go into adrenal crisis. They may present with Addison's disease and then develop the ALD picture later on or vice versa. Over the past 10 years we have begun to understand much more about the nature of the disease, its pathology, and underlying metabolic and molecular abnormalities. As yet there is no effective treatment, although some dietary trials are in progress.[3]

From a clinical point of view there are a number of variants. The most common variant is the childhood form described above. The condition may present in a similar form in adolescence and progresses in much the same way, although the whole process is slower. The condition may also present as a slowly progressive spastic paraparesis which is associated with adrenal dysfunction, so called adrenomyeloneuropathy,[4] here too the paraparesis may precede the Addison's disease. Occasionally an adult may present with a dementia. Although the disease is usually progressive, some patients have phases when the illness plateaus. Moser and Moser have given a very complete description of clinical variants.[5]

The full blown disease appears to be confined to males. There is often a family history of affected boys to suggest an X linked pattern of inheritance. Although female carriers are usually asymptomatic, some have clinical symptoms.[6] What is typical of ALD is that there can be a great deal of variation of clinical severity, not only between families but within one family. One member of an extended family could have adrenomyeloneuropathy, another Addison's disease, and a third classical ALD.

Recently the underlying defect has been shown to be a disorder of peroxisomal metabolism.[7] Peroxisomes are subcellular organelles performing a variety of functions including peroxidation (whence the name derives), the synthesis of plasmalogens which involves acyl CoA:dihydroxyacetone phosphate acyltransferase (DHAPAT), degradation of bile acids and the break down by beta oxidation of very long chain fatty acids.[8] Peroxisomal disorders have come into prominence recently as the main cause of the Zellweger's group of diseases in some forms of which peroxisomes are absent.[9] [10] In ALD peroxisomes are present but there is a single peroxisomal enzyme defect now thought to be lignoceryl CoA synthetase.[11] The biochemical findings in ALD have now been well worked out and include a rise of very long chain fatty acids, particularly C26:O, C24:O, but no rise of bile acid intermediates, nor a deficiency of DHAPAT.[12] What is even more unusual than the variation within a family is that asymptomatic siblings of a propositus may be shown to have the full biochemical defect without [redacted]

may reduce the $C26{:}22$ fatty acid ratio to normal values. It [redacted]



[redacted]

NEW LOWER PRICE

Software from Oxford

OXFORD DATABASE OF PERINATAL TRIALS

Editor: Iain Chalmers

With references to over 3500 published reports of randomized controlled trials this database is an invaluable tool for clinicians and researchers.

Each reference includes key details such as entry characteristics of participants, interventions studied, outcome measures used, and more.

In addition there are over 250 overviews (meta-analyses) of results of trials.

☐ Two updates published annually
☐ Includes many trials which cannot be found through *Medicine* searches
☐ Network licences available

Hardware requirements: IBM PC or PS/2 (and compatibles) with 12Mb minimum hard disk storage.

Price: £250 (UK customers add VAT) plus £10 postage and packing for overseas customers.

For further information please contact:
Janet Caldwell
Customer Service Manager Electronic Publishing Oxford University Press Walton Street Oxford OX2 6DP
Tel. 0865 56767 ext.4949 Fax. 0865 56646

Calculate with confidence:

Confidence Interval Analysis (CIA) is a computer program that takes the sweat out of calculating confidence intervals. Devised by Martin Gardner, professor of medical statistics, MRC Environmental Epidemiology Unit, University of Southampton, the IBM compatible program is menu driven with easy access to each chapter and to the method required within each chapter. Topics covered include calculating confidence intervals for:

- means and their differences
- proportions and their differences
- regression and correlation
- non-parametric analyses

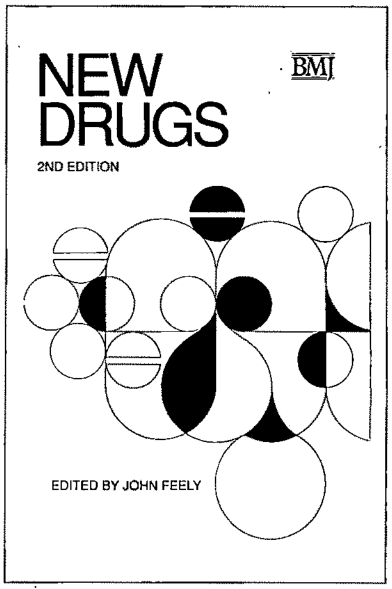
For each method relevant intermediate statistics and the required confidence interval are produced on the screen. Complete with its own manual, the program (available on $5\frac{1}{4}''$ or $3\frac{1}{2}''$ disk) may also be used in conjunction with the book ★*Statistics with Confidence*, which provides numerous worked examples.

£65.00. Educational establishments, research institutes, and the NHS — £45.95. Prices include VAT in the UK and air mail despatch abroad

★UK £7.95; Abroad £9.50
BMA members UK £7.45; Abroad £9.00

Please enclose payment with order (stating size of disk required), or send us full details of your MASTERCARD, VISA or AMERICAN EXPRESS credit card.

Order from: BRITISH MEDICAL JOURNAL
PO Box 295, London WC1H 9TE



Second edition
April 1991

xi+424 pages

UK £14.95
Abroad £18.00
BMA members
£13.95 or £17.00
including postage
by air abroad

New drugs are continually being developed and knowledge about existing drugs is constantly expanding, so it is essential, but difficult, for doctors to keep up to date with the latest developments. *New Drugs* describes the most important therapeutic advances of the past decade and discusses the drugs that will be in common use in the 1990s. Completely revised and updated, this second edition has been expanded to include 11 additional chapters. Its coverage of practical aspects of drug use, avoidance of adverse reactions and interactions, and prescribing at extremes of age makes it an invaluable guide for busy practitioners who want to get the best out of the new drugs currently available.

***Available from:* BRITISH MEDICAL JOURNAL,**
PO Box 295, London WC1H 9TE, ***medical booksellers or the BMJ bookshop in BMA House***

Please send me the following BMJ books:

____

____

I enclose________ BMA Membership No________

Please make cheques payable to **British Medical Journal** or debit my credit card (please tick box)

☐ Visa ☐ American Express ☐ Mastercard

Card No________________

Card expiry date________________

Signature________________

NAME________________

ADDRESS________________

____

____________ POSTCODE________

☐ Please send me a book catalogue

Archives of Disease in Childhood 1991; **66:** 833–837

ORIGINAL ARTICLES

The reliability of height and height velocity in the assessment of growth (the Wessex Growth Study)

L D Voss, T J Wilkin, B J R Bailey, P R Betts

Abstract

Both biochemical and auxological measurements can be used to assess growth. Quality control is routinely reported in laboratory studies, but the reproducibility of height measurements, and the height velocity data derived from them, is seldom considered. We have previously established our error and in this report we examine its implications for the screening of short children and subsequent monitoring of their growth. The 95% confidence interval for height for a 5 year old observed to be on the 3rd centile for height, spanned the 2nd–4th centile. However, the confidence interval for a 12 month height velocity appropriate to such a child spanned the 8th–52nd centiles, the lower limit pathological and the upper more than satisfactory. A single height velocity even over 12 months therefore lacks the precision to provide a reliable index of current growth in short children. Furthermore, serial height velocity calculations on a cohort of 78 short normal children showed no significant correlation from year to year, suggesting that velocity is also unable to predict future growth. Although the proportion of this cohort of short children lying beneath the 25th centile for velocity remained constant from year to year, the identity of the individuals comprising that proportion changed, a phenomenon which could be largely accounted for by the random error associated with height velocity. Our data suggest that, by the time a trend in abnormal velocity is reliably established, a deviation from the height centiles is clearly evident. Although velocity charts are attractive in concept, they seem to be no more discriminating than height charts in practice, and may be clinically deceptive unless interpreted with great care.

Poor growth in childhood may be a sign of poor health and deserves careful attention.[1 2] In the community short stature is usually identified by cross sectional screening of particular age groups, for example school entrants, and we have already drawn attention to the errors in screening associated with secular trend and poor calibration of equipment used.[3–5]

Clinically, difficulties have arisen with the interpretation of stress tests for growth hormone release, and paediatricians have reemphasised the value of auxological data to identify children who might benefit from growth hormone treatment.[6–8]

The measurement of height, like any other, is subject to error, but the size and implications of this error are seldom considered.[9] Moreover, height velocity has been promoted as a better means of expressing growth than height alone,[1 10 11] although it seems *a priori* unlikely that velocity, which is derived from height measurements, can be inherently more informative.

If velocity is to be used as an auxological tool, it should be recognised that there are very few data available on its reproducibility and the confidence with which paediatricians can use it for making clinical decisions. We have established our error of height measurement, and in this paper we examine its implications for the screening of short children and the subsequent monitoring of their growth.

Patients and methods

The clinical component of this study is based on the growth data of two cohorts of short children from the Wessex Growth Study, on or below the 3rd centile for height according to Tanner and Whitehouse standards,[12 13] who entered first school at the age of 5 during the school years 1985/6 and 1986/7, and who have been measured annually since by a single trained auxologist (LDV) using an electronic stadiometer (Holtain). Ethnic minorities, children with obvious organic disease, and children with psychosocial problems, identified by a behaviour questionnaire, were excluded from this study. Two years' height data are available for the remaining 78 short normal children (all of whom had normal thyroid function tests and normal concentrations of haemoglobin, creatinine, urea, and electrolytes) and 65 case controls of normal height (10th–90th centile) and same sex, age, and class at school. The mean height SD scores of the short children and their controls were −2·26 (0·32) and 0·47 (0·32) respectively.

Our error of measurement, expressed as the SD of a single height measurement (SDshm), was established as 0·25 cm from a series of calibration trials, the method for which has been reported previously.[5] The 95% confidence limits of a single *height* measurement (±2× SDshm) were therefore ±0·5 cm. The corresponding 95% confidence limits for expressing a 12 month height *velocity* were deduced from the formula: ±2 (SDshm) $\sqrt{2}$ cm/year, giving a value of ±0·71 cm/year. We applied these confidence limits to the Tanner and Whitehouse height and velocity standards appropriate to children of small and average height, in order to establish the error associated with these measurements expressed as absolute height (velocity), *height* SD scores (velocity SD scores) and height centiles (velocity centiles).

**Southampton General Hospital,
Department of Endocrinology**
L D Voss
T J Wilkin

Department of Paediatrics
P R Betts

Faculty of Mathematical Studies, University of Southampton
B J R Bailey

Correspondence to:
Ms L D Voss,
(Endocrine Section),
Medicine II, Level D,
South Block,
Southampton General Hospital,
Southampton SO9 4XY.

Accepted 19 February 1991

Results

CLINICAL OBSERVATIONS

Two consecutive 12 month measurements of height velocity data from the 78 short normal school entrants and their controls are shown in fig 1. Both groups of children had a normal distribution of height velocity. Although the mean velocity of the short children was significantly lower than that of their controls ($p<0{\cdot}001$) on both occasions, there was considerable overlap between them so that very few individual short children (six in year one and two in year two) could be distinguished from controls on the basis of a single 12 month velocity. Averaging the two years, 41% of the short normal children had a velocity below the 25th centile, and 15% a velocity below the 10th centile.

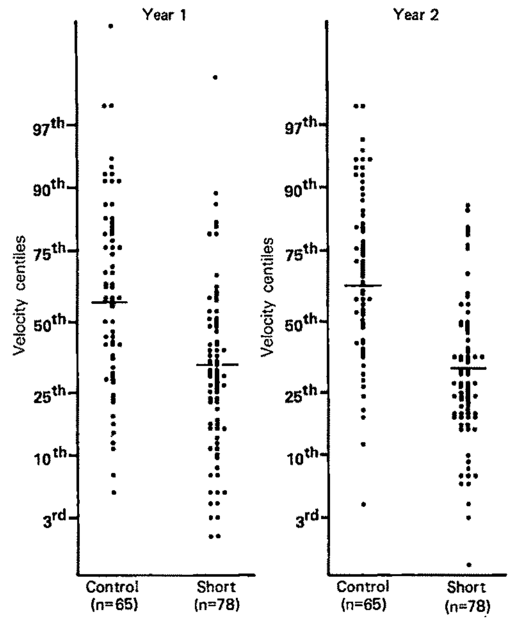


Figure 1 Scattergrams comparing the mean and distribution of 12 month height velocities of short normal (≤3rd centile for height) and control (10th to 90th centile for height) children 5 and 6 years of age. The data from two consecutive 12 month periods (year 1 and year 2) are shown.

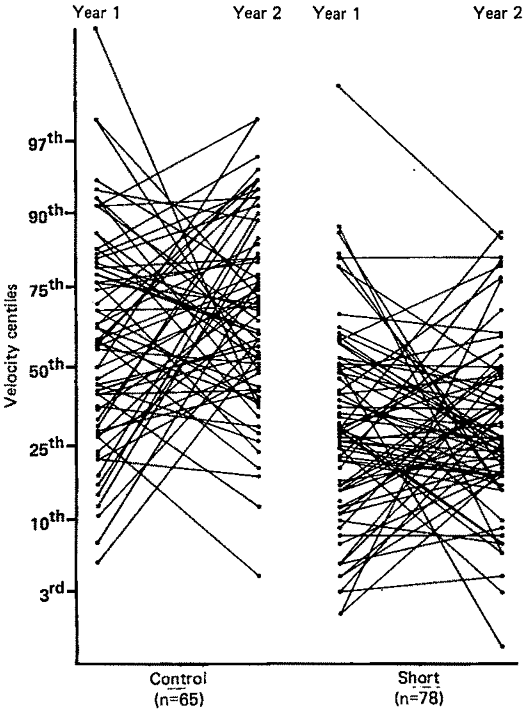


Figure 2 Correlations between consecutive 12 month height velocity values in the group of short normal children (≤3rd centile for height) and their controls (10th to 90th centile for height).

The 95% confidence limits for height and height velocity calculated for a short boy (3rd centile for height)

Growth data:	
At age 5·0 years	
Height (cm)	99·40
Height SD score	−1·88
Centile	3
At age 6·0 years	
Height (cm)	105·00
Height SD score	−1·87
Centile	3
Increment	5·60 cm/year
95% Confidence limits for height (±0·5 cm) at age 5·0 years:	
Height (cm)	98·90 to 99·90
Height SD score	−1·98 to −1·77
Centile	2nd to 4th
95% Confidence limits for 12 month height velocity (±0·71 cm/year) between age 5·0 and 6·0 years:	
Velocity cm/year	4·89 to 6·31
Velocity SD score	−1·39 to +0·04
Centile	8th to 52nd

Growth standards from Tanner and Whitehouse.[12 13]

There was no significant correlation between two consecutive 12 month velocity values in either the short children ($r=0{\cdot}17$, $p>0{\cdot}05$) or their controls ($r=0{\cdot}10$, $p>0{\cdot}05$) (fig 2). Although the proportion within each group which lay below the 25th and 10th centile respectively remained much the same from year to year, their identities largely changed. Only 14 (18%) of the short children lay below the 25th velocity centile and three (4%) below the 10th centile on *two* consecutive occasions. The corresponding proportions of the control group were one (1·5%) and none respectively.

IMPLICATIONS OF MEASUREMENT ERROR

The implications of a known error of measurement on the interpretation of height and height velocity data are adduced in the table. The range of centiles and SD scores crossed by the 95% confidence intervals for height and height velocity were calculated for a short boy, growing on the 3rd centile for height, between the ages of 5 and 6 years. The confidence intervals spanned a much wider range of velocity centiles (8th-52nd) than height centiles (2nd-4th) (fig 3).

The confidence intervals will be wider than those illustrated in cases where the error of measurement is greater than that reported here. The need for each auxologist to establish his or her error of measurement in the manner we have previously suggested is clear,[5] and fig 4 provides a reference chart from which the confidence limits corresponding to a given SDshm can be determined.

Finally, fig 5 illustrates the true height and height velocity for a (theoretical) slow growing 5 year old child plotted over three years from school entry. Even were the child to retain the 10th centile for velocity throughout (an unlikely event), the precision is such that no individual value can be reliably distinguished from the 25th centile. A trend to low velocity could be deduced from two successive values below the 25th centile,[11] but by this time (age 7 years), a

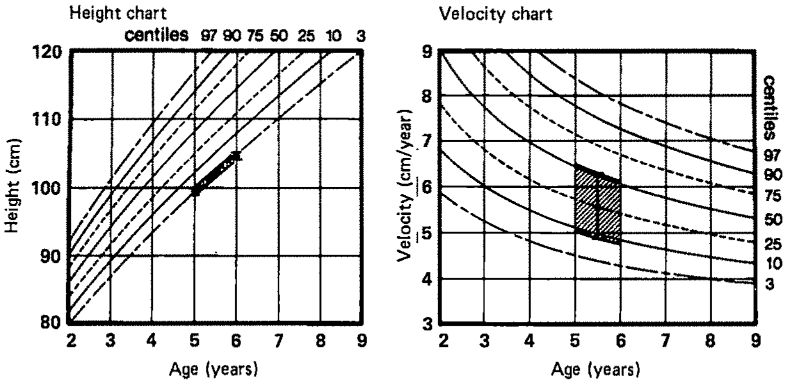


Figure 3 Tanner and Whitehouse height and velocity centiles on which have been plotted the 95% confidence intervals appropriate to a child between the age of 5 and 6 years, growing steadily along the 3rd centile for height, given a SD of a single height measurement of 0·25 cm.

departure from the 3rd centile for height is clearly evident. This is an idealised example. In practice, the wide fluctuations in successive velocity values illustrated in fig 2 are liable to occur, making the clinical interpretation of velocity data more difficult still.

FOOTNOTE

The 95% confidence interval for a *change* in velocity (acceleration/deceleration) can be derived from the formula $v_2 - v_1 \pm 2$ (SDshm) $\sqrt{6}$ cm/year/year. (The difference in velocity being based on three observations each one year apart.) Given an SDshm of 0·25 cm, a change in velocity of at least 1·22 cm/year/year would therefore have to be recorded to represent reliably a change. In practice, this means an acceleration to the 80th centile for a short 5 year old previously growing along the 25th centile for velocity (that is, 3rd centile for height). Anything less could be random error, and the reporting of responses to height-promoting treatment should be qualified accordingly.

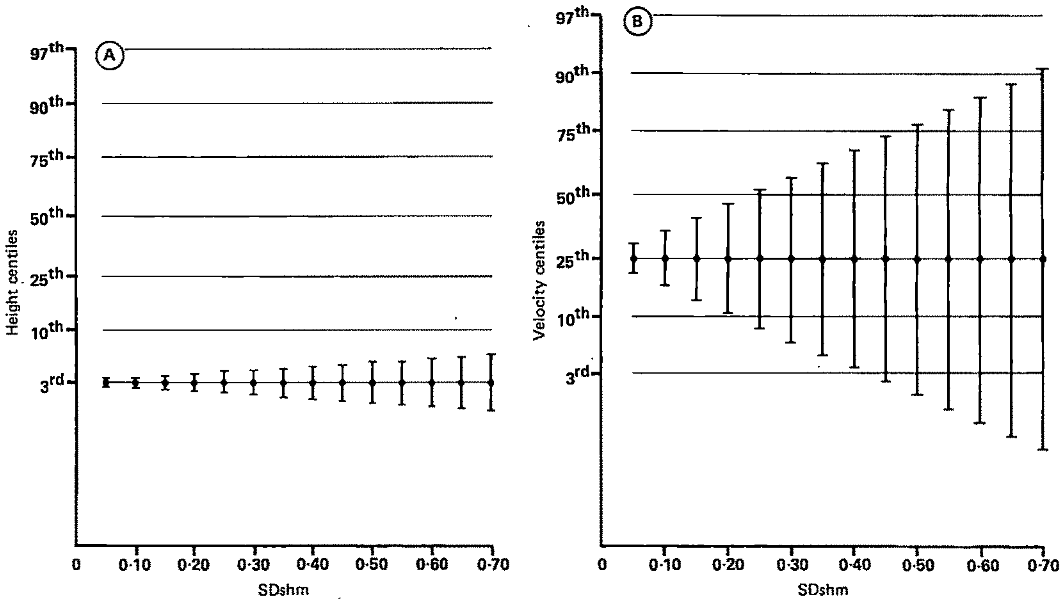


Figure 4 The 95% confidence intervals for (A) height and (B) 12 month height velocity data which correspond to a range of SDs for a single height measurement (SDshm) varying from 0·1 to 0·7 cm. The illustration corresponds to a child of 5 years growing along the third centile for height (25th centile for velocity), but the data can be moved up and down the ordinate axis as appropriate.

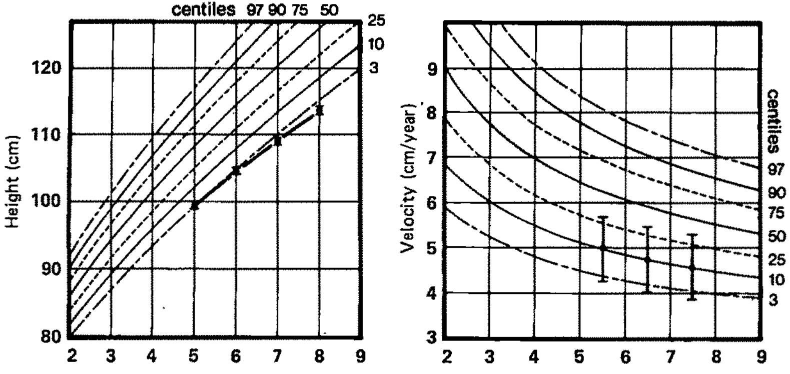


Figure 5 The appearance on height and velocity charts of the same data from a boy who was on the 3rd centile for height when first seen on his fifth birthday, and who grew slowly along the 10th centile for velocity over the next two years. The 95% confidence intervals for height and velocity corresponding to an SDshm of 0·25 cm are shown.

Discussion

This report does not deny height velocity a role in the auxological assessment of children, but it does seek to demonstrate that velocity is no more informative than height measurements alone, by establishing the confidence intervals appropriate to each. Because they are plotted on a magnified scale (0–24 cm rather than 45–195 cm as on a height chart), differences in velocity centile appear more convincing to the eye than the corresponding changes in height. But what appears to be gained in sensitivity is lost in reliability, as the error attaching to velocity is proportionately greater. The aim of this study was to explore the practical implications of the difference in reliability between height and velocity data.

In the Wessex Growth Study we were concerned to identify all school entrants in two health districts whose height lay below the 3rd centile.[4] The error, expressed as the SD for a single height measurement, was 0·25 cm and gave 95% confidence limits which correspond to the 2nd to 4th centile.[5] Our screening procedure, based as it was on a single height measurement, might therefore be expected to include a small number of children whose true height lay above the 3rd centile and to exclude a similar number from below.

For statistical reasons a short normal child who grows along the 3rd centile for height proceeds (on average) along the 25th centile for velocity.[7] We have shown that, with an SDshm of 0·25 cm, which is comparable with that quoted by Tanner[14] and less than that shown by Prader *et al*,[15] the confidence limits attaching to the 25th centile for velocity span the 8th–52nd centile. A velocity on the 8th centile would be considered pathological, while a velocity on the 52nd centile, corresponding to a child of average height, would be more than adequate for a small child. These measurements were taken by an experienced auxologist; if height were measured with less precision on a less reliable instrument, the confidence limits would be greater to the degree shown in fig 4. The error in velocity will be greater still if measurements are made less than 12 months apart.[14] First, an interval of just four months, as has been recommended,[16] would by itself triple the lengths of the confidence intervals illustrated. Second, measurements less than 12 months apart introduce seasonal variation. Diurnal variation will not influence the confidence intervals we have derived for height and height velocity, which were all based on measurements taken at the same time of day, but may be a further source of error when following up children in the clinic, where appointment times differ.

Although the distribution of the height velocities of the short children was predictably lower than that of the taller control children, there was such overlap that velocity could not be safely used to identify slow growers. On average, only about 5% of the short normal children on or below the 3rd centile for height had a growth velocity over 12 months below the range appropriate to the controls. Although the proportion of 'slow growers' defined by the 25th velocity centile remained fairly constant from year to year, the individuals represented in this proportion changed, and there was no correlation in the growth velocities of individuals from year to year. Thus velocity in small children not only fails to reflect previous growth,[4] but it also fails to predict future growth.

It has been suggested that two consecutive velocity values *below* the 25th centile will identify poor growth.[11] This, however, is a calculation based on a model child drawn from the whole population. All normal children below the 3rd centile for height already average less than the 25th centile for velocity (see above), so that the velocity centile appropriate to a diagnosis of poor growth is not fixed, and will vary with the height of the child. It may be possible to identify a significantly reduced velocity by applying trend statistics to the chance of lying on or below a particular centile on two or more occasions.[11] However, two or preferably three measures of velocity would be needed to do this, implying at least two or possibly three years of observation. By this time, as we have shown, a fall on the height centile chart will be evident.

Our data show that in clinical practice a substantial proportion (18%) of short normal children are observed to fall below the 25th centile for velocity over two successive years compared with only 1% of taller controls. This, and the fact that a single 12 month velocity measurement can, through its imprecision, appear to be very low, should raise questions about the use of height velocity to determine the need for growth hormone treatment.[6–8]

From a pragmatic point of view there may be much to commend the concept of height velocity: it can be a useful tool for evaluating group data. For the assessment of individual children, however, velocity cannot be expressed with sufficient precision. It cannot identify poor growth more quickly and does not improve upon the height data from which it is derived. As we have pointed out previously, the variability is largely (95%) due to the elasticity of children who are of no fixed height from one moment to the next.[5] We conclude that there is considerable imprecision in the auxological assessment of growth, and we have been unable to demonstrate that either height or height velocity is superior to the other. When screening for poor growth or monitoring response to treatment in individuals we are inclined to recommend the height chart for its simplicity and (provided it is properly maintained) its relatively low risk of being misinterpreted. The fact remains, however, that making clinical decisions on the basis of short term growth data, whatever its form, may be misguided and there is a clear need for growth surveillance to start at an early age and to continue throughout childhood.

LDV is generously supported by Kabi Pharmacia UK Ltd and Sweden AB and TJW by the Wellcome Trust. We thank Ms BA Peddle and Mrs J Mulligan for expert preparation of the manuscript.

1 Parkin JM. The short child. In: Brook CGD, ed. *Clinical paediatric endocrinology*. Oxford: Blackwell Scientific Publications, 1989:96–117.
2 Mahoney CP. Evaluating the child with short stature. *Pediatr Clin North Am* 1987;34:825–49.
3 Voss LD, Wilkin TJ, Betts PR. Do we need new growth charts? *Lancet* 1987;ii:447–8.
4 Voss LD, Walker J, Lunt H, Wilkin TJ, Betts PR. The Wessex growth study: first report. *Acta Paediatr Scand [Suppl]* 1989;349:65–72.
5 Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement. *Arch Dis Child* 1990; 65:1340–44.
6 Brook CGD. Treatment of growth deficiency. *Clin Endocrinol (Oxf)* 1988;30:197–204.

7 Hindmarsh PG, Brook CGD. Auxological and biochemical assessment of short stature. *Acta Paediatr Scand [Suppl]* 1988;**343**:73–6.
8 Milner RDG. Which children should have growth hormone therapy? *Lancet* 1986;i:483–5.
9 Cameron N. The methods of auxological anthropometry. In: Falkner F, Tanner JM, eds. *Human growth.* 2nd Ed. New York: Plenum, 1986;3:3–46.
10 Tanner JM. Use and abuse of growth standards. In: Falkner F, Tanner JM, eds. *Human growth.* 2nd Ed. New York: Plenum, 1986;3:95–109.
11 Brook CGD, Hindmarsh PC, Healy MJR. A better way to detect growth failure. *BMJ* 1986;**293**:1186.
12 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. *Arch Dis Child* 1966; **41**:454–71.
13 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. Part II. *Arch Dis Child* 1966;**41**:613–35.
14 Tanner JM. Physical development. *Br Med Bull* 1986;**42**: 131–8.
15 Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age. *Helv Paediatr Acta* 1988;Suppl 52:3–33.
16 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;**66**:85–7.

Treating tuberculosis

In 1983, 452 children were treated for tuberculosis in England and Wales. Four hundred and one of those had chest or lymph node disease and the treatment they were given was described in *Archives* in 1989.[1] The results of treatment were good but concern was expressed about variability in drug dosages and treatment duration and about possible overusage of ethambutol and underusage of pyrazinamide. It was pointed out that there was little information about the use of short course chemotherapy in children.

The November 1990 issue of *The Pediatric Infectious Disease Journal* contains two important reports of treatment trials and an excellent review article by Starke on pages 785–793.

The first of the trials was done in Papua New Guinea (Biddulph, pages 794–801) and is by far the largest yet reported, involving 639 children. For the first two months treatment was given in hospital using four drugs (rifampicin, isoniazid, pyrazinamide, and streptomycin) given daily and for the subsequent four months two drugs (rifampicin and isoniazid) were given twice a week under professional supervision. Despite high rates of default and non-compliance the results showed that six months' treatment is effective. Less than 2% of the children who completed a six month course relapsed and most of those had been irregular with their treatment.

The other trial was done in India (Kumar *et al*, pages 802–6) and involved 76 children. Thirty seven were given twice weekly treatment throughout, for the first two months with three drugs (rifampicin, isoniazid, and pyrazinamide) and for the next four months with two drugs (rifampicin and isoniazid). Thirty nine children were given daily treatment with three drugs for two months followed by twice weekly treatment with two drugs for four months. All treatment was given under professional supervision. Both treatment regimens were highly effective (>95% cure) and there were no relapses over two years of follow up. No serious side effects of the drugs requiring changes in treatment were encountered.

The advantages of three drug short (six month) course treatment include more rapid loss of infectivity in open disease, less time in which to be non-compliant, fewer resources required for treatment monitoring, and broader drug cover for resistant organisms. There seems to be no advantage in adding streptomycin. Extrapulmonary disease can be treated in the same manner but meningitis or bone and joint disease may need longer courses (see Starke, above).

The drug treatment of tuberculosis is a classical case for audit. There is no case to be made out for the therapeutic maverick. As recommendations change from time to time with the better use of old drugs and the introduction of new ones, my own practice is to ask a respiratory physician to look over my shoulder occasionally to make sure I'm still on the accepted track. The occasions on which it is useful to consult an adult orientated physician get fewer but this is still one of them.

ARCHIVIST

---

1 Medical Research Council Tuberculosis and Chest Diseases Unit. Management and outcome of chemotherapy for childhood tuberculosis. *Arch Dis Child* 1989;**64**: 1004–12.

Archives of Disease in Childhood 1991; **66:** 838–840

Growth prognosis and growth after menarche in primary hypothyroidism

S Pantsiotou, R Stanhope, M Uruena, M A Preece, D B Grant

Abstract

The long term growth of 20 girls and nine boys with juvenile primary hypothyroidism was studied until they reached final height. At diagnosis the girls had a mean age of 8·8 years (range 3·0–13·0); mean bone age was 5·4 years. The mean age of the boys at diagnosis was 9·5 years (range 3·7–14·2); mean bone age was 6·3 years. The patients were treated with thyroxine 100 μg/m²/day and serum thyroxine concentrations were maintained in the normal range. During treatment the rate of skeletal maturation exceeded the change in chronological age. Initial mean height SD score for bone age before treatment in the girls was +0·59 and after 11 years of treatment fell to −0·55. Mean height SD score for bone age in the boys decreased from +1·6 to −0·87 during treatment.

In the girls the onset of puberty was 1·2 years later than the normal population but the duration of puberty was reduced. Mean age (SD) of menarche was 13·8 (1·7) years. The pattern of growth in girls with treated hypothyroidism was abnormal as growth continued after menarche, at a time when normal girls have almost stopped growing. During the second year after menarche our patients still had a mean growth velocity of 4·1 cm/year.

Our data suggest that juvenile primary hypothyroidism results in a permanent height deficit. In addition, there is a loss of the normal harmony between growth and sexual maturation in girls, despite adequate treatment, in that growth continues for much longer after menarche than in normal girls.

Acquired juvenile primary hypothyroidism often has an insidious onset characterised by gradual deceleration and eventual cessation of growth.[1] The initiation of thyroxine treatment in primary hypothyroidism allows rapid 'catch up' growth.

It has been suggested that catch up growth is complete and final height prognosis is realised.[2] However, there has not been a comprehensive evaluation of growth in children with juvenile hypothyroidism to test this assumption. Analysis of long term growth in congenital hypothyroidism also suggests that catch up is limited when treatment is delayed.[3] Children treated after the age of 1 year by Bucher *et al* had accelerated skeletal development and reduced long term growth.[3] It has been demonstrated that the treatment of prolonged juvenile acquired hypothyroidism results in a permanent height deficit which is related to the duration of thyroxine deficiency before treatment.[4] It is not known whether the skeletal system responds in an exaggerated manner to normal replacement doses of thyroxine but there are artifacts in the methodology of the estimation of bone age.[5]

There is a normal harmony (or consonance) of the sequence of sexual maturation and its relationship to the spontaneous growth acceleration of puberty.[6] Usually, peak height velocity in girls during the pubertal growth spurt occurs at breast stage 2 to 3 and menarche occurs concomitant with breast stage 4 when growth velocity has decelerated.[7] In this retrospective study we have examined growth after menarche in girls with treated primary hypothyroidism after the initial catch up phase of growth had been completed.

**Institute of Child Health,
30 Guilford Street,
London WC1N 1EH**
S Pantsiotou
R Stanhope
M Uruena
M A Preece
D B Grant

Correspondence to:
Dr Stanhope.

Accepted 4 March 1991

Patients and methods

We have examined the records of patients with juvenile primary hypothyroidism seen over the previous 23 years. Patients were included if they had primary hypothyroidism from prepuberty and no other endocrinopathy or serious illness. All our patients had growth data available from the commencement of treatment to maturity. These criteria were satisfied in 20 girls and nine boys. Unfortunately measured parental heights were unavailable in many of our patients. In the analysis of growth during puberty three girls who had menarche just before diagnosis and subsequently grew a mean of 13·5 cm are excluded as it was not possible to distinguish between catch up growth due to thyroxine treatment and normal pubertal growth.

In most patients a standard dose regimen of thyroxine 100 μg/m²/day was used.[8] Serum concentrations of thyroxine and thyroid stimulating hormone were determined every six months during treatment to test short term compliance and point to the necessity for an alteration of thyroxine dose.

Long term growth was analysed by comparison of longitudinal changes in statural growth and skeletal maturation. The growth standards were those of Tanner and Whitehouse.[9] [10] Bone age was determined by the method of Tanner *et al.*[11] Pubertal development was staged by the method of Tanner.[12] Testicular size was assessed using a Prader orchidometer.[13]

In normal girls peak height velocity occurs at a mean of 1·4 years before menarche when growth deceleration is maximal.[7] The correlation of age at peak height velocity and age at menarche is approximately 0·9.[7] We used these data for the analysis of growth during puberty, using the mean growth velocity from the data of Tanner and Whitehouse for normal girls.[9 10] Differences between mean values were tested by using the *t* test for unpaired samples.

Results

Serum concentrations of thyroxine and thyroid stimulating hormone were maintained in the physiological range in all patients and there was no biochemical evidence of overtreatment.

In the girls, mean height SD score for bone age before treatment was +0·59. At the age of 17·5 years, after 11 years of treatment, mean height SD score for bone age was −0·55 ($p<0·01$, fig 1). In the boys the mean initial height SD score for bone age was +1·6 and after nine years of treatment at the age of 16·5 years, height SD score for bone age decreased to −0·87 ($p<0·02$, fig 2). At attainment of adult stature all the patients, except for one girl, were below the 50th centile.[9 10]

In the boys with treated hypothyroidism the onset of genital development occurred at a mean age of 13·3 (1·4) years, 1·7 years later than normal population.[14] Their sequence of sexual maturation and its relationship to the growth spurt was indistinguishable from normal boys. By contrast, the pubertal growth spurt in the girls with treated hypothyroidism had different characteristics from those of normal girls.[9 15] The onset of puberty (breast stage 2) was a mean of 12·4 years, 1·2 years later than normal girls.[15] Mean age of menarche in our patients was 13·8 years (range 10·9–16·7) compared with 13·5 years in normal girls. Menarche occurred at breast stage 4 in our patients, so that the time from the onset of puberty to menarche was reduced in the girls with primary hypothyroidism. Although the intensity of the growth spurt was indistinguishable from normal girls, the pattern of growth differed (fig 3). Growth continued at a faster rate than in normal girls and at menarche mean growth velocity was 7·2 cm/year. During the first year after menarche, when normal girls have almost stopped growing, our patients had a mean growth velocity of 5·1 cm/year and during the second year a velocity of 4·1 cm/year (fig 3). However, the girls demonstrated a normal sequence of acquisition of secondary sexual characteristics, which excluded abnormal pubertal development characterised by isolated breast development and raised concentrations of follicle stimulating hormone.[16]

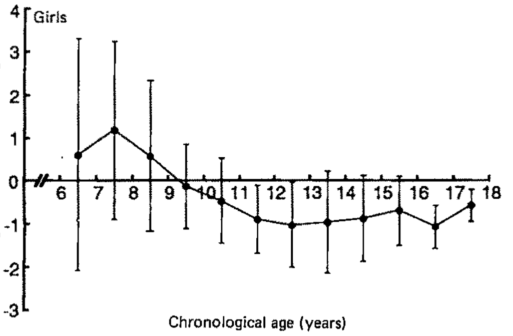


Figure 1 Height SD score for bone age for 20 girls with primary hypothyroidism during thyroxine treatment. Circles represent mean, horizontal bars 1 SD.

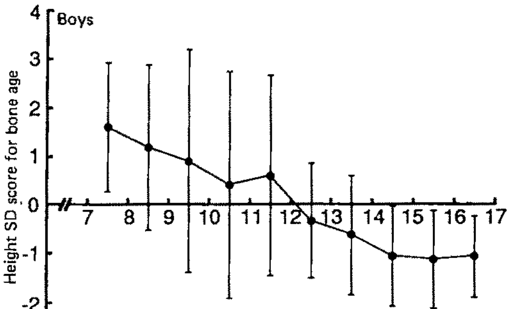


Figure 2 Height SD score for bone age for nine boys with primary hypothyroidism during thyroxine treatment. Circles represent mean, horizontal bars 1 SD.

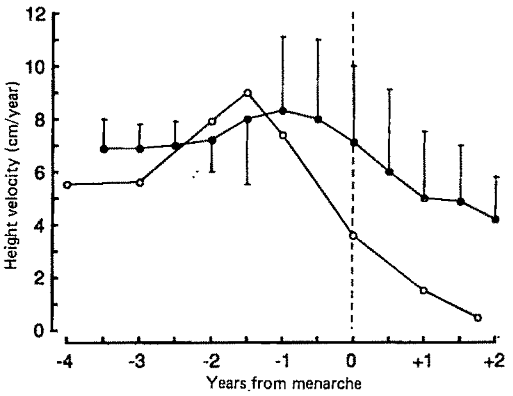


Figure 3 Growth velocity data from 17 girls with primary hypothyroidism treated with thyroxine, related to menarche. Solid circles and horizontal bars represent mean (SD) for patients with hypothyroidism. Open circles represent mean data for normal girls from Tanner et al.[10 15]

Discussion

We have demonstrated that catch up growth is incomplete after treatment of long standing juvenile hypothyroidism. Our patients did not attain their genetic growth potential as assessed both by height SD score for bone age. The final height of all the patients, except one, was below the mean for the normal population. Certainly precocious or abnormal sexual maturation were not contributory factors in our patients.[16] Our findings, in terms of the long term growth sequela of juvenile acquired hypothyroidism, are similar to those of Rivkees *et al*.[4]

We have based our assessment of height prognosis on height for bone age SD score, predominantly as height at diagnosis in our patients was far below the normal range. Methods of bone age assessment and height prediction vary in their accuracy according to age and diagnosis.[17] Bone age assessment compares the morphology of the epiphysis and its relationship with the metaphysis.[11] Certainly hypothyroidism disproportionately affects the epiphysis and it is not surprising that such assessments may deliver low scores. This 'artifact' may explain why bone age scores at diagnosis in primary hypothyroidism are disproportionately delayed to a greater extent than height age.

Non-compliance may be important because of either over or under treatement. It was impossible to exclude intermittent non-compliance as a contributory factor in our patients. Occasional blood tests, taken at planned clinic visits, assess only short term events and offer no reassurance of longer term compliance. Prolonged severe hypothyroidism may diminish the potential for catch up growth. It may be that delay in the onset of treatment is a critical factor in limiting catch up growth and emphasises the need for early recognition of this disorder.[18]

We do not know what leads to disproportionate catch up in bone age compared with height advance during early treatment. Histomorphometric studies in adults with primary hypothyroidism have shown exaggerated osteoclastic activity and reduced bone mass. This finding may be related to calcium deficiency and is associated with low concentrations of stimulated calcitonin.[19 20] It is probable that multiple factors are involved.

In the girls growth at puberty both in duration and quality was abnormal. Our patients had an abnormal pattern of growth after menarche with loss of the normal relationship between growth and pubertal maturation. The girls continued to grow after menarche even though initial catch up growth had been completed. We can offer no explanation of why girls with juvenile primary hypothyroidism are shorter than expected, despite growing faster and for longer during puberty. The use of a gonadotrophin releasing hormone analogue, to delay the timing and duration of puberty, may be a possible therapeutic approach but results in short normal children have been disappointing.[21]

These observations indicate that the treatment of acquired primary juvenile hypothyroidism is associated with compromised final height despite adequate replacement treatment. In girls after the initial phase of catch up growth associated with thyroxine treatment, both growth and its relationship to pubertal development remain abnormal. Despite the age at onset of primary hypothyroidism, 'adequate' replacement treatment with thyroxine does not lead to a normalisation of growth and its relationship to sexual maturation.

1 Talbot NB, Sobel EH, McArthur JW, Crawford JD. *Functional endocrinology from birth through adolescence.* Cambridge, Mass: Harvard University Press, 1952:1–51.
2 Tanner JM. Catch-up growth in man. *Br Med Bull* 1981;**37**: 233–8.
3 Bucher H, Prader A, Illig R. Head circumference, height, bone age and weight in 103 children with congenital hypothyroidism before and during thyroid hormone replacement. *Helv Paediatr Acta* 1985;**40**:305–16.
4 Rivkees SA, Bode HH, Crawford JD. Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. *N Engl J Med* 1988;**318**:599–602.
5 Preece MA, Cox L. Estimation of biological maturity in the older child. In: Bitles A, Collins KJ, eds. *Biology of human ageing: symposium proceedings.* Cambridge: Cambridge University Press, 1986:67–80.
6 Stanhope R, Brook CGD. The clinical diagnosis of disorders of puberty: the loss of consonance. *Br J Hosp Med* 1986; **35**: 57–8.
7 Tanner JM. Growth and endocrinology in the adolescent. In: Gardner L, ed. *Endocrine and genetic disease of childhood.* Philadelphia: WB Saunders, 1969:14–60.
8 Abbassi V, Aldige C. Evaluation of sodium L-thyroxine (T4) requirement in replacement therapy of hypothyroidism. *J Pediatr* 1977;**90**:298–301.
9 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part I. *Arch Dis Child* 1966;**41**:454–71.
10 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966;**41**:613–35.
11 Tanner JM, Whitehouse RH, Cameron N, *et al. Assessment of skeletal maturity and prediction of adult height.* 2nd Ed. London: Academic Press, 1983.
12 Tanner JM. *Growth at adolescence.* 2nd Ed. Oxford: Blackwell Scientific Publications, 1978.
13 Zachmann M, Prader A, Kind HP, Haflinger H, Budliger H. Testicular volume during adolescence. *Helv Paediatr Acta* 1974;**29**:61–72.
14 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in boys. *Arch Dis Child* 1970;**45**:13–23.
15 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;**44**:291–303.
16 Pringle PJ, Stanhope R, Hindmarsh P, Brook CGD. Abnormal pubertal development in primary hypothyroidism. *Clin Endocrinol (Oxf)* 1988;**28**:479–86.
17 Preece MA. Prediction of adult height: methods and problems. *Acta Paediatr Scand* 1988;**347**(suppl):4–11.
18 Abbassi V, Rigterink E, Cancellieri RP. Clinical recognition of juvenile hypothyroidism in the early stage. *Clin Pediatr (Phila)* 1980;**19**:782–6.
19 Body J-J, Demeester-Mirkine N, Borkowski A, Suciu S, Corvilain J. Calcitonin deficiency in primary hypothyroidism. *J Clin Endocrinol Metab* 1986; **62**:700–3.
20 Coindre J-M, David J-P, Reviere L, *et al.* Bone loss in hypothyroidism with hormone replacement. A histomorphometric study. *Arch Intern Med* 1986;**146**:48–53.
21 Stanhope R, Brook CGD. The effect of GnRH analogue on height prognosis in growth hormone deficiency and normal puberty. *Eur J Pediatr* 1988;**148**:200–2.

[redacted]

Abridged Prescribing Information
SABRIL▼ Tablets

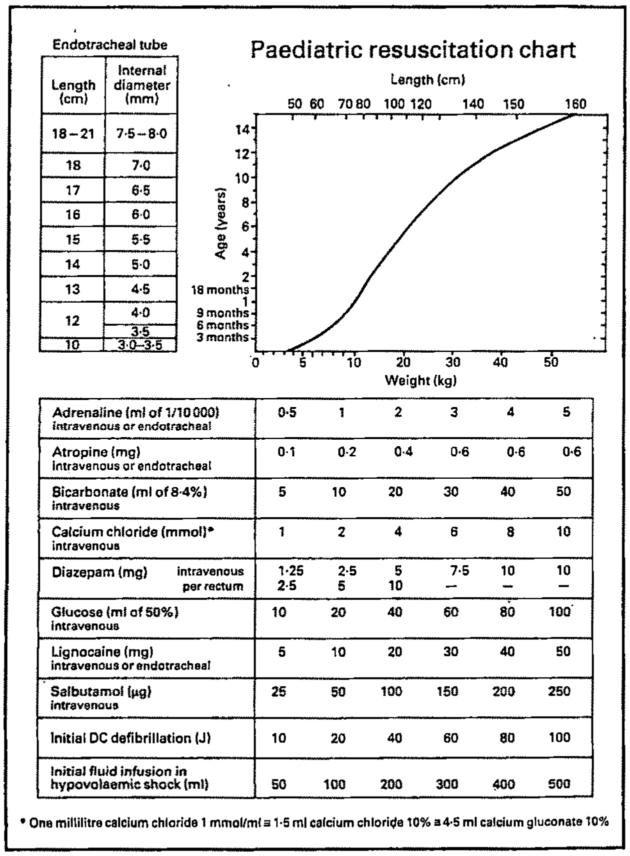
Presentation: White tablets with a breakline marked SABRIL, each containing 500mg vigabatrin.
Uses:
Indications: Treatment of epilepsy not controlled by other antiepileptic drugs.
Dosage and Administration: Oral administration once or twice daily added to the patient's current therapeutic regimen.
Adults: Recommended starting dose 2g/day. Increased or decreased in 0.5g or 1.0g increments depending upon clinical response and tolerability. Maximum 4g/day.There is no direct correlation between plasma concentration and efficacy.
Children: Recommended starting dose 1g/day in ages 3-9 years and 2g/day if older.
Elderly: Consider dose reduction in patients with impaired renal function.
Contra-indications, Precautions, Warnings etc
Use in pregnancy and lactation: Contra-indicated.
Precautions: Abrupt withdrawal may lead to rebound seizures.Caution in patients with history of psychosis or behavioural problems.Caution in elderly patients, particularly creatinine clearance below 60ml/min. Reduce dose and monitor closely for adverse events.
Warnings: Vigabatrin causes intramyelinic oedema in the brain white matter tracts of animals but there is no evidence of this in man. However, monitor patients for neurological changes. See the full product data sheet.
Effects on driving ability: Drowsiness has been seen and patients should be warned.
Side effects: Are mainly CNS related. Aggression and psychosis have been reported and a previous history of psychosis or a behavioural problem appears to be a predisposing factor. Other reported events: drowsiness and fatigue, dizziness, nervousness, irritability, depression, headache and less commonly confusion, memory disturbance and vision complaints; also weight gain and minor gastrointestinal side-effects. Also in children excitation and agitation.Some patients may experience an increase in seizure frequency with vigabatrin, particularly those with myoclonic seizures.Tests have not revealed evidence of neurotoxicity in humans.Lab data do not indicate renal or hepatic toxicity. Decreases in SGOT and SGPT have been observed. Chronic treatment may lead to a slight decrease in haemoglobin.
Drug Interactions: Are unlikely. A gradual reduction of about 20% in plasma phenytoin concentration has been observed. No clinically significant interactions with carbamazepine, phenobarbitone or sodium valproate.
Legal Category: POM
Package Quantities: Blister strips of 10 in cartons of 100.
Product Licence Number: PL 4425/0098
NHS Price: £46.00
Date of Preparation: November 1990.
You must refer to the full prescribing information before administering Sabril. Further information including full product data sheet is available from the Licence Holder: Merrell Dow Pharmaceuticals Ltd, Lakeside House, Stockley Park, Uxbridge, Middlesex, UB11 1BE

Reference:
1. Livingston J *et al* (1989) Br J Clin Pharm 27 (Suppl 1): 1095–1125

JOB NO: SAB 0691

TRADEMARKS: Sabril, Merrell, Dow.

**MERRELL
DOW**



Paediatric resuscitation chart

Endotracheal tube

Length (cm)	Internal diameter (mm)
18–21	7·5–8·0
18	7·0
17	6·5
16	6·0
15	5·5
14	5·0
13	4·5
12	4·0
	3·5
10	3·0–3·5

Adrenaline (ml of 1/10 000) intravenous or endotracheal	0·5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal	0·1	0·2	0·4	0·6	0·6	0·6
Bicarbonate (ml of 8·4%) intravenous	5	10	20	30	40	50
Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
Diazepam (mg) intravenous	1·25	2·5	5	7·5	10	10
Diazepam (mg) per rectum	2·5	5	10	—	—	—
Glucose (ml of 50%) intravenous	10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal	5	10	20	30	40	50
Salbutamol (μg) intravenous	25	50	100	150	200	250
Initial DC defibrillation (J)	10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)	50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml ≡ 1·5 ml calcium chloride 10% ≡ 4·5 ml calcium gluconate 10%

A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

Poster: UK £3.50; Abroad £4.50 including packing and postage, by air abroad.
Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.
Credit cards are accepted: ACCESS, VISA, AMERICAN EXPRESS (please give full details)

BMJ BRITISH MEDICAL JOURNAL, BMA HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR

Archives of Disease in Childhood 1991; **66**: 841–843

Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone

A Papadimitriou, S Wacharasindhu, K Pearl, M A Preece, R Stanhope

Abstract

Forty six prepubertal boys who had constitutional growth delay were treated with oxandrolone. Mean age at the onset of treatment was 11·9 years (range 9·0–14·0) and bone age delay was 1·9 'years'. The dose of oxandrolone used was a mean of 0·05 mg/kg (range 0·03–0·18) for a mean of 0·9 years (range 0·2–3·6). Height velocity increased from a mean (SD) before treatment of 4·0 (1·0) to 7·5 (1·2) cm/year with oxandrolone. Growth rate was sustained at 7·6 (2·2) cm/year in the period after treatment. Those boys who attained a testicular volume of 4 ml or greater at the end of the treatment period had the most pronounced sustained growth acceleration. Height for bone age SD score did not alter significantly from a mean of −1·0 before treatment to −1·2 after treatment.

Oxandrolone is a safe and effective treatment for prepubertal boys with constitutional growth delay.

Oxandrolone is an anabolic steroid that is effective in a low dose regimen for the treatment of constitutional delay of growth and puberty.[1] This is not a placebo effect[2] and does not decrease final height.[3] For psychological reasons such children may require treatment to improve their short term growth rate at an earlier stage of sexual maturation than would be expected for the spontaneous growth spurt of puberty.[1] Treatment alters the 'tempo' of their growth without altering final height prognosis.[1]

By definition, constitutional delay of growth and puberty requires short stature, delay of epiphyseal maturation, and pubertal delay (>2 SD). However, children who will progress to develop constitutional delay of growth and puberty can often be predicted at a much earlier age by their pattern of bone age maturation and growth delay (which we have described as constitutional growth delay). We believe it is important to treat such children at an early stage in order to anticipate and prevent more severe psychological problems during puberty. During the pubertal growth spurt growth is dependent on a combination of growth hormone and sex steroids.[4] We have substituted the latter by the use of an anabolic steroid in order to improve short term growth rate, and hopefully to induce a sustained growth acceleration, and to anticipate the boys' stature falling below the normal range at an age when emotional, educational, and physical development is at a premium.[5] [6] Recent data has pointed to the important psychological sequelae of constitutional delay of growth and puberty[7] and we have attempted to anticipate some of these problems.

Patients and methods

Clinical data from 46 patients with constitutional growth delay are shown in the table. Mean age for the onset of treatment was 11·9 years, which is almost the mean age for the onset of puberty in normal boys.[8] The height of all the boys was below the 3rd centile for chronological age, although one was just below the 10th centile. All had symptoms of psychological disturbance, which related to their short stature. Eight boys had mild asthma but had not been treated with systemic corticosteroids. None of the boys had any other medical disorders.

Most of the boys commenced oxandrolone treatment in a dose of 1·25 mg daily, although some (n=5) started at 2·5 mg per day. This calculated at a mean dose of 0·05 mg/kg (range 0·03–0·18). Duration of treatment was 0·9 years (range 0·2–3·6). Treatment was continued either until a 4 ml testicular volume was attained or until a satisfactory increment in height had been gained and the patient did not wish to continue treatment.

Growth was measured by standard anthropometric techniques[9] and bone age measured by the method of Tanner *et al.*[10] Testicular volume was assessed using a Prader orchidometer[11] and with experience 2, 3, and 4 ml volumes could be distinguished. Height SD score for bone age related height and epiphyseal maturation to the

Institute of Child Health,
30 Guilford Street,
London WC1N 1EH
A Papadimitriou
S Wacharasindhu
M A Preece
R Stanhope

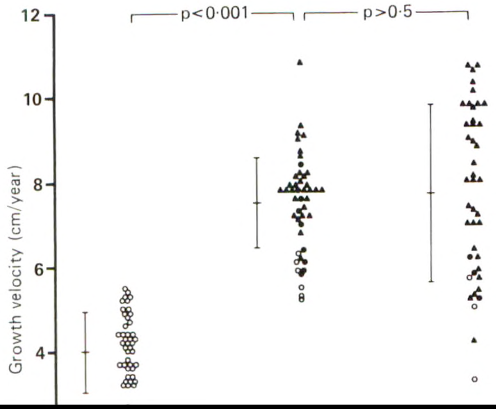
Farnborough Hospital,
Kent
K Pearl

Correspondence to:
Dr Stanhope.

Accepted 14 March 1991

Clinical and growth data on 46 prepubertal boys with constitutional growth delay treated with low dose oxandrolone. Results are mean (range) except for height SD score

	Before treatment (n=46)	*During treatment (n=46)*	*After treatment (n=43)*
Chronological age at onset of treatment (years)		11·9 (9·0 to 14·0)	
Duration of period (years)	0·8 (0·2 to 3·3)	0·9 (0·2 to 3·6)	0·8 (0·2 to 1·8)
Bone age delay (years)		−1·9 (−5·2 to −0·1)	
Time from start of treatment to onset of puberty (years)		0·8 (0·25 to 3·6)	
Height SD score for bone age	−1·0 (−3·0 to +1·7)		−1·2 (−3·7 to 1·3)
Mean (SD) change in height SD score for bone age from values before treatment			−0·2 (0·8)
p Value			>0·5



mean and SD of the normal population as a measure of height prognosis.[12 13] Statistical analysis was by paired *t* test.

Results

During oxandrolone treatment growth velocity increased from a mean (SD) of 4·0 (1·0) to 7·5 (1·2) cm/year, which was significant to a level of p<0·001. Forty of the boys entered puberty during the treatment period and these boys tended to grow at a faster rate than the six who remained prepubertal (fig 1). In the period after treatment the growth rate was sustained at a

[redacted]

oxandrolone for 3·6 years and demonstrated an appropriate advance in his epiphyseal maturation. None of the boys experienced adverse reactions during their course of treatment.

Discussion

Oxandrolone in prepuberty caused an effective increase in growth rate that was at a higher level in those boys who entered puberty during their course of oxandrolone treatment. Normal boys would not expect the commencement of their growth spurt to be until the attainment of 10 ml testicular volume (genitalia stage 3–4).[14] Oxandrolone treatment brought forward the timing of the growth acceleration, which was sustained in the post-treatment period, while allowing a normal pattern and rate of pubertal maturation. This was of therapeutic value to the boys as the treatment anticipated the growth deceleration that would have occurred as well as their probable late timing of the spontaneous growth spurt.[15] Boys with constitutional delay may experience enormous psychological diffi-

[redacted]

Although short courses of oxandrolone are effective in the treatment of constitutional delay of growth and puberty,[1] prolonged courses of oxandrolone, for about one year, are required in prepubertal boys with constitutionally delayed growth. Such longer courses do not lead to adverse side effects, as indeed such prolonged courses appear to be safe when used in girls with Turner's syndrome.[16] An alternative treatment regimen would be to use depot or oral testosterone preparations. The latter are irregularly absorbed from the gastrointestinal tract and the former may lead to a rapid induction of secondary sexual characteristics as well as an induced growth acceleration. In our experience the psychological benefits of a prolonged course of oxandrolone are significant and such treatment regimens are safe and effective.

1 Stanhope R, Brook CGD. Oxandrolone in low-dose for constitutional delay of growth and puberty in boys. *Arch Dis Child* 1985;**60**:379–81.

2 Stanhope R, Buchanan CR, Fenn GC, Preece MA. Double blind placebo controlled trial of oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988;**63**:501–5.

Archives of Disease in Childhood 1991; 66: 844–847

Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood

F Skovby, S Micic, B Jepsen, S O Larsen, B Hansen, L Tegllund, B N Pedersen

Abstract

A total of 3025 families with schoolchildren aged 6–8 years were offered pilot screening for familial hypercholesterolaemia by measurement of the concentrations of apolipoproteins A-1 and B in the children's capillary blood and by analysis of their family histories of early ischaemic heart disease. The concentrations of the apolipoproteins were determined by double rocket immunoelectrophoresis of an eluate of blood spotted on filter paper. Results were available from 2085 children. Because their B:A-1 ratio was above the 97·5 centile and their concentration of B was above the 99th centile, 54 children (2·6%) were selected to have their apolipoprotein concentrations reassessed. The 17 children (0·8%) whose values were persistently above the chosen cut off points, and all of their available first and second degree relatives, had fasting determinations of serum lipid concentrations carried out. Raised serum concentrations of low density lipoprotein cholesterol and an autosomal dominant pattern of hypercholesterolaemia were found in 12 children and 10 families, respectively, suggesting a higher incidence of familial hypercholesterolaemia than the reported 1:500. Further investigations among family members disclosed hypercholesterolaemia in 29 relatives. A family history of early ischaemic heart disease was elicited by questionnaire, and was positive in only five of the 12 schoolchildren with hypercholesterolaemia.

We conclude that analysis of apolipoproteins from capillary blood spotted on filter paper is suitable for screening for familial hypercholesterolaemia, and that this method is more efficient than screening based on family history.

Division of Clinical Genetics, Department of Pediatrics, University Hospital GGK 4062, 9 Blegdamsvej, 2100 Copenhagen, Denmark
F Skovby

Department of Neonatology, University Hospital, Copenhagen, Denmark
B Jepsen
L Tegllund

Pediatric Consultation Service, Copenhagen School System, Denmark
B Hansen

Department of Clinical Biochemistry, State Serum Institute, Copenhagen, Denmark
S Micic
S O Larsen
B N Pedersen

Correspondence to:
Dr Skovby.

Accepted 24 January 1991

Heterozygous familial hypercholesterolaemia has an overall incidence in various populations of about 1:500, making it one of the most common inborn errors of metabolism.[1] Affected adults have a significantly increased risk of early ischaemic vascular disease including fatal myocardial infarction. In people without known predisposition to hypercholesterolaemia, raised concentrations of total cholesterol and low density lipoprotein cholesterol, which are present from birth in familial hypercholesterolaemia,[2] are strongly correlated with early (20 years old) atherosclerotic lesions in the aorta and coronary arteries.[3] The apparent onset of atherosclerosis in childhood makes the detection and proper management of children with hypercholesterolaemia (including familial hypercholesterolaemia) a matter of concern to many paediatricians.

This paper describes a pilot screening programme for familial hypercholesterolaemia among schoolchildren by measuring the concentrations of apolipoproteins A-1 and B in capillary blood.

Patients and methods

In August 1987, 3025 families with children aged 6–8 years who were starting in the first grade of the Copenhagen school system were offered the chance to participate in a pilot screening programme for the detection of familial hypercholesterolaemia. The parents were asked to answer a questionnaire about the occurrence of coronary heart disease in their families. Upon completion of the questionnaire, the parents were requested to give their permission for blood samples to be taken from their child.

Capillary blood was obtained from the children without prior fasting between 8 am and 12 noon. About five drops of ear blood were collected on to filter paper (No 2992; Schleicher and Scholl), which was allowed to dry at room temperature for two hours, transported to the laboratory within six hours, and stored at 4°C in sealed plastic bags containing silica gel capsules until quantification of apolipoproteins on the next day.

Measurements were made by double rocket immunoelectrophoresis as previously described.[4] After determination of the centile values for apolipoproteins, all children with ratios of B:A-1 greater than the 97·5 centile or with a concentration of apolipoprotein B above the 99th centile were selected for repeat sampling of capillary blood and analysis of apolipoproteins. The children whose values were persistently above the chosen cut off points, and all their available first and second degree relatives, had venous blood taken after a 12 hour fast for analysis of the serum concentrations of total cholesterol, high density lipoprotein cholesterol, very low density lipoprotein cholesterol, and triglycerides as previously described.[5] Low density lipoprotein cholesterol was calculated as total cholesterol minus the sum of high density lipoprotein cholesterol and very low density lipoprotein cholesterol. If the serum concentration of low density lipoprotein cholesterol in a child was above the 95th centile for age,[5] additional analyses of the lipid profile were done at intervals of at least three weeks. A physical examination was made, and appropriate laboratory tests were done to exclude causes of secondary hyperlipidaemia. The children with hypercholesterolaemia were offered follow up care in the paediatric lipid clinic.

The parents were asked to complete a questionnaire about the incidence of chest pains or coronary occlusions in themselves or their relatives (parents, sibling, aunts, and uncles). Information about the age at the time of the first symptom was requested. A positive family history of early ischaemic heart disease was defined as angina pectoris or myocardial infarction before the age of 50 in men, and before the age of 60 in women.

The study protocol was approved by the science and ethics committee of the Copenhagen City Hospitals.

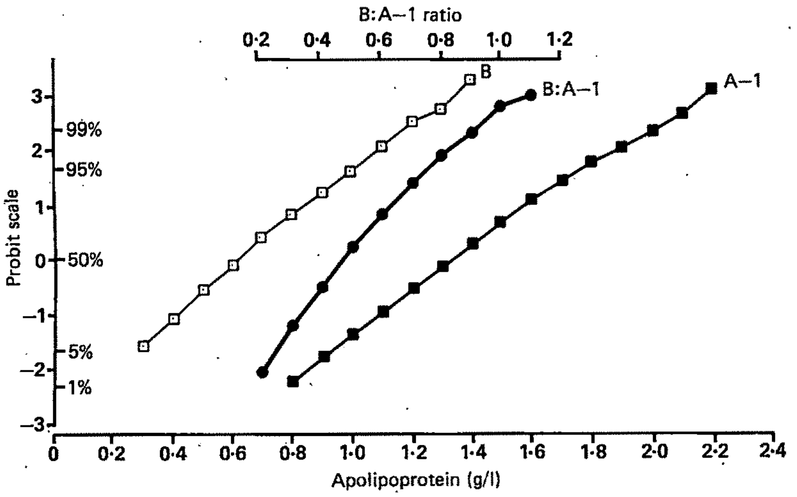
Results

Of the 3025 questionnaires distributed, 2657 (87·8%) were returned; the parents of 2166 (71·6%) gave permission for capillary blood samples to be taken from their children. No information was given about the reasons why 491 families (16·2%) did not consent to the sampling of blood.

Measurements of apolipoproteins A-1 and B were successful in 2085 schoolchildren 6–8 years old. The cumulative distributions of the observations and the B:A-1 ratio are shown as probit diagrams in the figure. The distributions of apolipoproteins B and A-1 are close to normal, whereas the distribution of the ratio is slightly skewed. Children with a B:A-1 ratio above the 97·5 centile (about 0·83) had their capillary apolipoprotein concentrations checked. Of the 47 children, 12 had a B:A-1 ratio that was persistently above 0·83. Only one of these 12 children had serum concentrations of total cholesterol and low density lipoprotein cholesterol below the 95th centile for Danish children of the same age group.[5] The table shows the serum lipid concentrations in the other 11 children and their parents. In 10 families both the child and one parent had biochemical signs of type IIa hyperlipidaemia. One of these families was already known to have familial hypercholesterolaemia (case 87, table).

Among the 19 children with an apolipoprotein B concentration above the 99th centile (about 1·2 g/l), 12 also had a B:A-1 ratio of more than 0·83. On repeat measurement of capillary apolipoproteins, 11 of the 19 children had concentrations of apolipoprotein B consistently in the top centile; six of the 11 children also had a B:A-1 ratio of more than 0·83. Subsequent analysis of serum lipid profiles from the 11 children showed that seven had type IIa hyperlipidaemia. Only one of the seven children (case 110, table) had not been detected because two subsequent B:A-1 ratios were above 0·83. Conversely, this criterion for selection identified three children with abnormally high concentrations of serum lipids but with an apolipoprotein B concentration below the 99th centile (cases 98, 99, and 106, table).

Extensive family investigations disclosed 29 close relatives between 1 and 59 years of age with previously undiagnosed hypercholesterolaemia indicated by concentrations of low density lipoprotein cholesterol above the 95th centile for age and sex.[6] In six families such cases were identified in at least three generations. Three of four other families in which hypercholesterolaemia was documented in only two generations were immigrant families from which the grandparents were not available for lipid analysis; in the fourth family a paternal grandfather had died from a myocardial infarction at the age of 55. Thus in 10 families there was an autosomal dominant pattern of type IIa



Cumulative distributions of apolipoprotein A-1, apolipoprotein B, and the ratio B:A-1 (probit scales; n=2073). The curves represent results from the first measurement of capillary apolipoproteins, excluding the 12 children later identified as having hypercholesterolaemia.

Concentrations of capillary apolipoproteins and fasting serum lipid profiles in children with hypercholesterolaemia and their parents

Case No	*Child*						*Father*				*Mother*				*Family history of ischaemic heart disease*
	Apolipoproteins (g/l)		*Cholesterol (mmol/l)*			*Triglycerides (mmol/l)*	*Cholesterol (mmol/l)*			*Triglycerides (mmol/l)*	*Cholesterol (mmol/l)*			*Triglycerides (mmol/l)*	
	B:A-1 ratio	*B*	*Total*	*Low density lipoprotein*	*High density lipoprotein*		*Total*	*Low density lipoprotein*	*High density lipoprotein*		*Total*	*Low density lipoprotein*	*High density lipoprotein*		
87	0·93	1·30	8·2	6·7	1·1	1·2	10·1	8·7	1·0	0·9	Not measured	Not measured	Not measured	Not measured	Yes
96	0·95	1·32	7·2	5·2	1·4	1·3	7·2	5·5	1·0	2·6	4·3	2·3	1·3	1·0	No
97	0·99	1·29	6·2	4·8	1·1	0·7	6·0	4·2	1·1	1·5	4·9	3·0	1·6	0·8	Yes
98	0·96	0·93	6·0	4·2	1·2	1·2	9·0	6·6	1·6	1·4	4·9	3·1	1·4	0·9	No
99	0·96	0·98	6·5	4·4	1·1	2·1	8·6	6·7	1·0	2·1	5·3	3·8	1·5	0·6	Yes
101	0·96	1·12	6·3	5·2	1·0	0·6	9·6	8·2	0·8	1·5	4·0	2·1	1·7	0·5	No
102	1·03	1·57	8·3	6·9	1·0	1·1	8·3	5·7	1·7	2·2	9·8	8·0	0·9	1·9	No
103	1·38	1·68	9·6	8·3	1·0	0·8	10·2*	9·0	0·8	1·4	Not measured	Not measured	Not measured	Not measured	Yes
105	1·50	2·01	8·8	7·6	1·0	0·7	5·6	4·1	1·2	0·9	11·6*	10·5	1·1	0·5	No
106	0·91	1·07	7·0	5·6	0·9	1·3	13·2	9·1	1·0	5·7	6·3	4·7	1·4	0·7	No
107	1·31	1·37	7·6	6·4	1·1	0·6	6·5*	5·2	0·7	1·5	4·6	3·2	1·1	0·6	No
110	0·80	1·39	6·8	4·9	1·5	0·8	5·8	4·4	1·1	0·8	6·9	4·6	1·8	1·1	Yes

*Xanthelasmata.

hyperlipidaemia. In the remaining two families (cases 97 and 107, table) parental lipid analyses showed concentrations of low density lipoprotein cholesterol below the 95th centile for age and sex.

The children listed in the table were all normal on physical examinations, except for one child who was obese (case 98). Laboratory investigations of the causes of secondary hyperlipidaemia were unrevealing. All but one of the families were interested in counselling and follow up for the children with hypercholesterolaemia. Information about risk factors for atherosclerotic vascular disease and about the principles behind a diet to lower blood cholesterol concentrations was offered by the physician in the paediatric lipid clinic. Particular emphasis was placed on a reduction of the intake of saturated fats from meat and dairy products, because both of these feature largely in the traditional Danish diet. The children were then seen at three to six month intervals and height, weight, and lipid profile were measured. After six to 12 months a three day dietary history was recorded by a dietitian, and the daily intakes of energy, saturated and polyunsaturated fats, and cholesterol were calculated. Further advice depended upon the reduction of total and low density lipoprotein cholesterol concentrations achieved and on the dietary history. Two years after diagnosis no child had required hyperlipidaemic drugs.

Analysis of the 2657 completed questionnaires disclosed a history of early ischaemic heart disease in 398 families (15·0%). Of the 491 families who did give permission for blood samples to be taken from their children, 27 gave a positive family history by questionnaire (5·5%). Only five of the 12 children identified as having hypercholesterolaemia by apolipoprotein analysis had a positive family history of early ischaemic heart disease on the questionnaire.

Discussion

According to official recommendations screening of children for hypercholesterolaemia should be directed at high risk groups—that is, those with a family history of cardiovascular disease or hyperlipidaemia.[7 8] Several concerns have been raised about a low risk, population based approach, including the cost of techniques for measuring cholesterol and the ability of the tests to detect all children with raised low density lipoprotein cholesterol concentrations. Andersen *et al* have shown that it is feasible to screen newborns for hyperlipoproteinaemia by measuring very low density lipoprotein and low density lipoprotein cholesterol concentrations in cord blood, a method which is impractical for routine neonatal screening.[9] More recently, newborn infants have been screened for familial hypercholesterolaemia by measurement of apolipoprotein B in capillary blood.[10] The methods used in the present study were developed for the same purpose—that is, to screen newborns for familial hypercholesterolaemia using blood from the filter paper currently used in Denmark to screen for phenylketonuria and congenital hypothyroidism. The method used for analysis of apolipoproteins is based on immunological quantification of these substances from small amounts of capillary blood easily obtained from infants, and it is suitable for screening a large number of children.[4]

Familial hypercholesterolaemia is characterised by raised serum low density lipoprotein cholesterol concentration. Direct measurement of this lipoprotein is difficult, and an estimate based on the serum values of other lipid fractions requires larger amounts of blood than are normally obtainable from capillary samples. Several studies have suggested that the circulating concentration of apolipoprotein B, the apoprotein of low density lipoprotein, is a better predictor of premature coronary artery disease than is the total plasma cholesterol concentration.[11] The absolute concentrations of apolipoproteins in blood absorbed in filter paper cannot be determined accurately because the precise volume of blood is not known.[4] This difficulty is circumvented by the simultaneous measurement of apolipoprotein A-1 and the use of the B:A-1 ratio as the criterion for detection of familial hypercholesterolaemia. In capillary blood from 68 such patients aged 4–42 years we have previously found the B:A-1 ratio to be consistently above 0·90.[4] We therefore took the ratio of 0·83, or the 97·5 centile of our study group, as the threshold for recall so that we had a wide enough margin to avoid false negative results. Our data did not allow an estimate of the number of false negative results—that is we cannot find out how many children with B:A-1 ratios below 0·83 have hypercholesterolaemia. None the less, the unexpected high incidence of familial cases of hypercholesterolaemia (about 1:200 compared with the usually reported incidence of familial hypercholesterolaemia of about 1:500[1]) suggests that the number of false negative results is small. It is possible that some of the children detected have hypercholesterolaemia that is not low density lipoprotein receptor deficient heterozygous familial hypercholesterolaemia—for example, familial combined hyperlipidaemia or inherited defects of apolipoprotein B. Although the data presented in the table favour the diagnosis of familial hypercholesterolaemia in most cases, this can be confirmed only by direct assay of the number or the molecular structure of low density lipoprotein receptors in cells from affected patients.

Only five of the 10 children with documented parental hypercholesterolaemia had family histories of early ischaemic heart disease (table). The lack of such information in the other families could be explained in several ways. Many people with hypercholesterolaemia do not develop signs of coronary disease until they are in their sixties or later, and they would not have contributed to a positive family history by our criteria. A proportion of subjects heterozygous for familial hypercholesterolaemia live to old age protected by factors as yet unknown from their raised low density lipoprotein cholesterol concentrations and thus from fatal ischaemic heart disease.[12] Whereas the high familial correlation between early coronary deaths and familial hypercholesterolaemia makes a strong case for proper management of children with a positive family history, the need to identify and perhaps treat affected children without such a history is less obvious.[12] Finally, and most likely, there may have been under-reporting of ischaemic heart disease in the questionnaires because of the poor reliability of anecdotal family medical information.[13]

Screening of adults for hypercholesterolaemia is a controversial issue, let alone screening of children. In view of the serious long term prognosis, however, we believe that screening for familial hypercholesterolaemia is justified at any age. Dietary habits are established in childhood, and affected children are likely to benefit from a prudent diet; some may also benefit from medical treatment. Our results support the conclusion drawn from several recent studies of hypercholesterolaemia in children—namely, that selective screening based on family history is inadequate as only about half of all children with hypercholesterolaemia are identified.[14–16] In contrast to screening of adults for hypercholesterolaemia, the usefulness of total serum cholesterol concentration as a screening test for raised low density lipoprotein cholesterol concentrations in children is limited by the higher concentrations of high density lipoprotein cholesterol in many children and adolescents than in adults.[17] Apolipoprotein B has test characteristics superior to those of total cholesterol concentration in detecting raised concentrations of low density lipoprotein cholesterol in serum.[18] Our findings confirm the feasibility of using measurement of capillary apolipoproteins as a screening test for hypercholesterolaemia in children.

We dedicate this paper to the memory of Dr GE Andersen, who initiated the study. Inger Jeppesen, Lis Vejbæk, Winni Sabro, and Alice Nielsen gave us superb technical assistance. Our colleagues in the paediatric consultation service of the Copenhagen school system were most helpful in the collection of blood samples. Financial support was provided by Helsefonden and the Danish Heart Association.

1 Goldstein JL, Brown MS. Familial hypercholesterolemia. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited disease.* New York: McGraw-Hill, 1989:1215–50.

2 Kwiterovich PO Jr, Levy RI, Frederickson DS. Neonatal diagnosis of familial type II hyperlipoproteinemia. *Lancet* 1973;i:118–21.

3 Newman WP, Freedman DS, Voors AW, *et al.* Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa heart study. *N Engl J Med* 1986;**314**:138–44.

4 Micic S, Arends J, Nørgaard-Pedersen B, Christoffersen K, Andersen GE. Simultaneous quantification by double rocket immunoelectrophoresis of apolipoprotein A-I and B in blood spotted on filter paper. *Clin Chem* 1988;**34**:2452–5.

5 Ibsen KK, Lous P, Andersen GE. Lipids and lipoproteins in 350 Danish schoolchildren, ages 7 to 18 years. *Acta Paediatr Scand* 1980;**69**:231–3.

6 Appleyard M, ed. The Copenhagen city heart study: Østerbroundersøgelsen. *Scand J Soc Med* 1989;**17**(suppl 41):80–4.

7 American Academy of Pediatrics, Committee on Nutrition. Indications for cholesterol testing in children. *Pediatrics* 1989;**83**:141–2.

8 British Cardiac Society. *Report of British Cardiac Society working groups on coronary disease prevention.* London: British Cardiac Society, 1987.

9 Andersen GE, Lous P, Friis-Hansen B. Screening for hyperlipoproteinemia in 10 000 Danish newborns. *Acta Paediatr Scand* 1979;**68**:541–5.

10 Blades BL, Dudman NPB, Wilcken DEL. Screening for familial hypercholesterolaemia in 5000 neonates: a recall study. *Pediatr Res* 1988;**23**:500–4.

11 Editorial. Apolipoprotein-B and atherogenesis. *Lancet* 1988;**i**:1141–2.

12 Heiberg A, Slack J. Family similarities in the age at coronary deaths in familial hypercholesterolaemia. *BMJ* 1977;**ii**:493–5.

13 Napier JA, Metzner H, Johnson BC. Limitations of morbidity and mortality data from family histories—a report from the Tecumseh community health study. *Am J Public Health* 1972;**62**:30–5.

14 Griffin TC, Christoffel KK, Binns HJ, McGuire PA, The Pediatric Practice Research Group. Family history evaluation as a predictive screen for childhood hypercholesterolemia. *Pediatrics* 1989;**84**:365–73.

15 Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Parental history of cardiovascular disease as an indication for screening for lipoprotein abnormalities in children. *J Pediatr* 1989;**115**:186–94.

16 Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. *Pediatrics* 1989;**84**:751–5.

17 Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Serum total cholesterol for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa heart study. *Pediatrics* 1990;**85**:472–9.

18 Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Measurement of apolipoprotein B as a screening test for identifying children with elevated levels of low-density lipoprotein cholesterol. *J Pediatr* 1990;**117**:358–63.

Archives of Disease in Childhood 1991; **66:** 848–853

Gastro-oesophageal reflux and respiratory function in infants with respiratory symptoms

F J Hampton, U M MacFadyen, C S Beardsmore, H Simpson

Abstract

This study aimed to define the incidence and severity of gastro-oesophageal reflux (GOR), as measured using 24 hour oesophageal pH monitoring, in 38 infants with recurrent respiratory symptoms and to relate these findings to measures of respiratory function. Twenty one infants had a pH under 4 for more than 5% of the time (one definition of abnormal GOR) and nine had GOR exceeding age related normal values. Maximum expiratory flow at functional residual capacity was reduced in 37 infants, airways resistance was raised in 19 infants, and thoracic gas volume was abnormal in 11 infants.

There was no association between indices of GOR and measures of lung function whether assessed by correlation or by χ^2 analysis for normal versus abnormal values. However, individual infants appeared to have respiratory symptoms produced by GOR. This suggests that host responsiveness to GOR may be of greater relevance than the amount of GOR.

Gastro-oesophageal reflux (GOR) is sometimes regarded as a key underlying cause of recurrent and chronic respiratory symptoms, both in adults[1-3] and in children.[4-16] In infants GOR might be relatively more important as posseting is common,[17] and the effect of conventional bronchodilator treatment on cough and wheeze is unimpressive.[18 19] Surprisingly few previous studies addressing the association between GOR and respiratory symptoms have been restricted to infancy.[7] Information about the frequency of the association between the two and the nature of any possible cause and effect relationship remains incomplete.

In many studies patients have been selected on the basis of a history compatible with GOR, a poor response to treatment, or anomalies in their clinical course such as frequent episodes of lung collapse or consolidation on chest radiography. These series have included children with a range of respiratory disorders making it difficult to reach precise conclusions. We have tried to minimise potential bias by selecting infants presenting with recurrent or chronic respiratory symptoms that were not caused by readily definable lung disease, such as bronchopulmonary dysplasia or cystic fibrosis, and without the imposition of other restrictions. We postulated that, were the association of respiratory symptoms and GOR confirmed, objective indices of respiratory and GOR severity would be directly related. We therefore aimed to determine the incidence and severity of GOR and of respiratory function abnormalities in this group and to investigate a possible association between them.

Patients and methods

CASE SELECTION

All infants aged less than 16 months presenting as general practitioner referrals to the paediatric outpatient department or admitted to hospital with cough and/or wheeze were considered for the study. The cough or wheeze was either chronic (over six weeks) or recurrent (each episode lasting longer than one week or occurring more than once a month). The study was approved by the ethical committee of the Leicestershire Health Authority. Exclusion criteria included mechanical ventilation in the newborn period, previous thoracic operations, or discovery of an underlying disorder on investigation (other than GOR). Investigations were performed as clinically indicated and no patients were found to have tuberculosis, cystic fibrosis, cardiac disease, or an immunocompromising disorder. One patient was excluded on account of a severe debilitating neurological disorder from which he subsequently died. Several potentially eligible infants were not included as their parents declined the invitation to participate in the study on the grounds that their children had relatively mild symptoms. Forty infants began the study but two were withdrawn when they removed the pH probe after a few hours and their parents did not wish it to be replaced.

The final study group from whom full data were available comprised 38 infants, 21 boys and 17 girls, aged 3 to 15 months, mean age 8 months. Three had been born prematurely but had not been ventilated. Table 1 summarises their clinical and radiography findings. Most had wheezing as their major symptom. In seven cases the first episode of wheezing occurred during acute bronchiolitis (when they were positive for respiratory syncitial virus). In six others bronchiolitis appeared to be the initial illness but virological data were not available. All infants had at least one chest radiograph and when clinically indicated some had further films taken. A single abnormal radiograph was seen in 11 infants, patchy collapse or consolidation in seven, and diffuse peribronchial thickening in four; two other infants had recurrent episodes of consolidation confirmed on radiography. Twenty four infants had a family history of atopic disorders (asthma, hay fever, eczema) in first degree relatives. Smoking in the home was reported for 30 infants of whom 21 had also been exposed in pregnancy.

Department of Child Health, University of Leicester
F J Hampton
U M MacFadyen
C S Beardsmore
H Simpson

Correspondence to:
Professor H Simpson,
Department of Child Health,
University of Leicester,
Clinical Sciences Building,
Leicester Royal Infirmary,
PO Box 65,
Leicester LE2 7LX.

Accepted 7 February 1991

Table 1 Classification of infants by history and findings on radiography

	Wheeze (n=33)		*Cough (n=5)*	
	Continuous (n=9)	*Episodic (n=24)*	*Continuous (n=4)*	*Episodic (n=1)*
Previous bronchiolitis:				
Yes (RSV+)	1	6		
Yes	3	3		
No	5	15	4	1
Chest radiography:				
Normal:				
Yes (RSV+)	1	4 (3)		
Yes	1	2 (2)		
No	4 (3)	11 (6)	2 (1)	
Diffuse changes:				
Yes (RSV+)		1		

[redacted]

additional measure of 'normal' was used. By defining the upper limit of normal for the reflux index for the total time either as RI=5% or RI score=4, two overall results of normal or abnormal were given to each pH study.

During the pH studies parents and nurses were asked to note the timing and duration of any symptoms, particularly episodes of wheeze or cough.

MEASUREMENT OF RESPIRATORY FUNCTION

Assessment of respiratory function consisted of occlusion for thoracic gas volume measurement. At least five representative breaths were chosen from the charted and computerised records to calculate airways resistance by conventional methods.[28,29] Specific conductance was calculated by dividing the reciprocal of airways resistance (conductance) by thoracic gas volume.

Respiratory function tests were expressed as a percentage of previously published predicted values based on the infant's length.[29,30] Thoracic gas volume was described as abnormal if it was over 120% or under 80% and very abnormal if over 140%. Airways resistance was considered raised if over 120% and very high if over 200%. Specific conductance was described as low if under 80% and very low if under 50%. $\dot{V}$maxFRC was graded at less than 80%, 50%, and 25%.

METHODS OF COMPARISON

Each measure of GOR was compared with each measure of respiratory function using Pearson correlation. This was then repeated using only the results from infants with abnormal GOR. Then a series of χ^2 tests for normal versus abnormal results was performed using both definitions of normal and abnormal for GOR. The χ^2 tests were also performed with only the extreme lung function test results classified as abnormal. These multiple comparisons run a high risk of demonstrating apparently significant results by chance but as it was uncertain which of the values might be relevant it was felt that this was a suitable initial approach. Any result appearing significant in this way would have to be retested in a new study.

Results

Completed data for GOR variables and respiratory function measures were obtained for all 38 infants studied. Twenty one infants had abnormal GOR as defined by a reflux index over 5% and nine had a reflux index score more than 4. The normal data of Vandenplas and Sacre-Smits included no infants aged 8·5 to 14 months[22] so the four infants in this age range were compared with the group closest in age, in all cases the younger group. All had an RI score less than 4 in this comparison and so were called normal, although they scored more than 4 on values for the older group. Using the normal values of Vandenplas and Sacre-Smits 25 infants had at least one of the four variables which was abnormal.

Three infants had a large thoracic gas volume (all >140%) and eight a small one (<80%). Nineteen infants had a high airways resistance (>120%) and nine very high (>200%). Results of $\dot{V}$maxFRC showed only one infant had a value >79% predicted, 12 between 50 and 79%, 14 between 25 and 49%, and 11 under 25%.

No correlations were found between any of the measures of reflux and any of the respiratory function test results whether the group as a whole was considered or only those with abnormal GOR. When using χ^2 for normal versus abnormal values there was also no association observed (table 2).

Eleven infants had a median pH at night lower than that by day but their respiratory function tests did not differ from those of the other infants. Similarly there was no difference in respiratory function between the nine infants with an abnormal mean duration of reflux at night (>4 minutes) as defined by Jolley *et al*[7] and the others.

Comparing the 13 infants with at least one abnormal chest radiograph with the 25 who only ever had a normal chest radiograph no differences in reflux variables were seen. The group with abnormal radiography had a higher thoracic gas volume, median 104% versus 86% (p=0·01), but these medians are both within the normal range.

Differences in history were analysed using the Mann-Whitney test. Separating the infants by their family history of atopic disorders (one or more first degree relatives with asthma, eczema, or hay fever) revealed an unexpected difference in the amount of GOR. Fifteen of the 28 reflux variables analysed were significantly higher in the group with no family history of atopy. This is demonstrated in figs 1 and 2 for the RI and the RI score. The median RI in those with a family history of atopy was 4·7% and in those without 11·7% (p=0·0004) and the 95% confidence intervals (CI) for the difference were 3 to 10·8. For the score the median value for those with a family history of atopy was 2·2 and for those without 4·6 (p=0·0003) with 95% CI for the difference being 0·9 to 2·9. As seen in the figure the only abnormal RI scores are in the group without a family history of atopy.

No significant differences were found in respiratory function test results between the groups with and without a family history of atopy. Division by smoking exposure or history of bronchiolitis demonstrated no differences in either respiratory function or reflux variables.

The data on the timing of respiratory symptoms during the pH study was incomplete, largely because symptoms did not occur or were constant but possibly in some cases because they were not recorded. Two infants with variable symptoms had a strong temporal association between these and their GOR. The first had a family history of asthma and a normal pH study by all criteria (RI=2·4%); wheezing was reported during all the brief episodes of reflux during her 24 hour study and she later develo-

Table 2 Results of respiratory function tests versus pH studies

	Thoracic gas volume			*Airways resistance*			*$\dot{V}$maxFRC*				*Specific conductance*		
	Low	*Normal*	*High*	*Normal*	*High*	*Very high*	*<25%*	*<50%*	*<79%*	*Normal*	*Very low*	*Low*	*Normal*
RI >5%	5	16	0	12	5	4	5	8	7	1	3	6	12
RI <5%	3	11	3	7	5	5	6	6	5	0	7	3	7
RI score >4	2	7	0	6	1	2	1	4	3	1	2	1	6
RI score <4	6	20	3	13	9	7	10	10	9	0	8	8	13

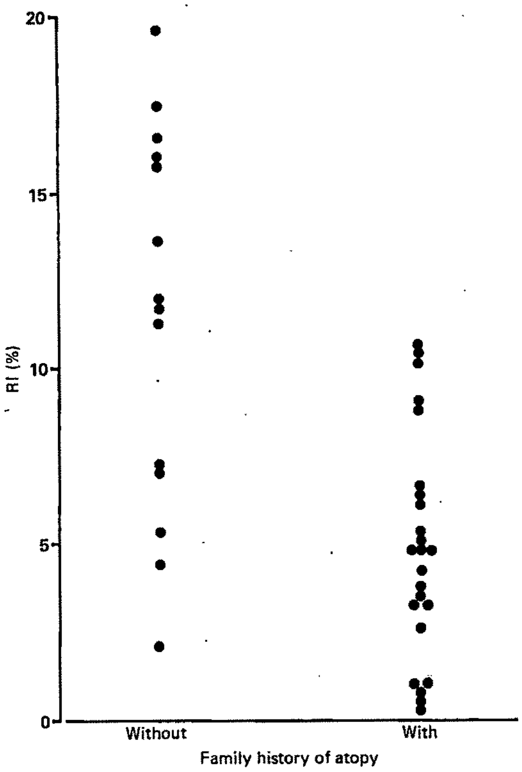


Figure 1 Reflux index (RI) for the total time in infants with and without a family history of atopy (upper limit of normal 5%).

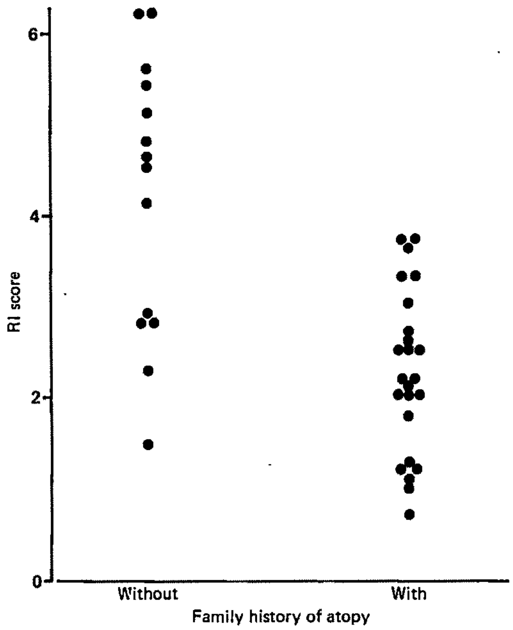


Figure 2 Reflux index (RI) score in infants with and without a family history of atopy (upper limit of normal 4).

ped wheeze induced by acid fruit juice drinks. In the other infant, who also had a family history of atopy and who had moderately abnormal GOR (RI=6%), reflux episodes were associated with periods of tachypnoea recorded by his mother. The first of these infants had abnormal airways resistance, specific conductance, and $\dot{V}$maxFRC and the second a low thoracic gas volume and reduced $\dot{V}$maxFRC. A further infant, with no family history of atopy, appeared to have a link between GOR and respiratory symptoms. He had recurrent episodes of consolidation on radiography and significant GOR (RI=11%) but after having a Nissen's fundoplication he had no further episodes. His preoperative respiratory function tests were normal except for a $\dot{V}$maxFRC of 53% of predicted. He developed perioperative respiratory syncytial virus bronchiolitis and his postoperative $\dot{V}$maxFRC was 25% of predicted.

Discussion

Previous studies of the association between GOR and respiratory disease have selected children with particularly severe symptoms,[10 11] recurrent pneumonias suggestive of aspiration,[4] appreciable nocturnal symptoms,[16] or a combination thereof.[6 9 13] Where these features have not been used for selection a broad age range of children has been studied.[5 14] In selecting patients for this study we had two aims, firstly to limit the age of the children investigated to under 18 months and secondly to include all infants with chronic or recurrent respiratory symptoms in whom a specific underlying disease had not been identified.

The results obtained from this group provide the opportunity to speculate on the role of GOR in a uniform group of infants with moderate 'disease'. Within this group nearly all the infants had abnormal respiratory function tests, which is not surprising as they were selected for respiratory symptoms. A proportion of the infants also had excessive GOR, 21 (55%) had an RI of more than 5% and nine (24%) had an RI score over 4. Thus even when using the highest available normal values, more GOR occurred in this group than would be expected from a randomly selected group.

Exploring this association further, however, we found no relationship between the amount of acid GOR and the degree of abnormality of respiratory function tests. The pattern of GOR was also unrelated to respiratory function abnormalities. Jolley *et al* found that infants whose nocturnal reflux episodes had a mean duration of longer than four minutes had an improvement in their respiratory disease after surgery for GOR.[7] This measure of GOR was not associated with more abnormal respiratory function tests in our study. Vandenplas *et al* found that infants with respiratory disease had a lower mean pH value at night than during the day.[31] Using median pH values the 11 infants in this study whose median nocturnal pH was less than their daytime median did not have more severe respiratory function abnormalities than the others.

The differences we found in the amount of GOR between the infants with and without a family history of atopy are unlikely to have been due to chance as they occurred in 15 of the 28 variables and most were highly significant ($p<0{\cdot}01$). Taking the pH study results in isolation, without considering respiratory function or clinical features, it appeared that there may have been two groups of infants with different underlying problems. Infants with a family history of atopy may have represented one group whose respiratory symptoms were partly determined by inherited factors, such as atopy or bronchial hyperreactivity, while the others represented a group in whom respiratory symptoms were more likely to have been due to GOR. However, within each of the two groups there was no correlation between the amount of reflux and the severity of respiratory dysfunction suggesting that there are other reasons for the differences in results. In addition the observation that wheezing may be temporally related to minimal GOR suggests that even normal amounts of reflux may underly respiratory symptoms in the presence of predisposing host factors.

In the three infants described in detail there was a clear clinical connection between GOR and respiratory symptoms but the results of pH studies and respiratory function tests were unrelated. The infant with recurrent consolidation and excessive reflux had only minimal respiratory function abnormalities while the other two had more severe lung function abnormalities and less GOR. The lack of association between measures of GOR and respiratory function in these three infants reflects that found in the group as a whole and raises the possibility that this may mask a true link between the two.

There are several possible explanations for this lack of association. Respiratory function test changes resulting from GOR may not be present at the time of the tests or may not be detected by the tests performed. Studies in adults and older children have found that mimicking GOR with acid infused into the oesophagus did not influence baseline lung function tests but only bronchial reactivity, which we did not measure.[32–35] Another possibility is that the measurement of GOR was influenced by the confounding effect of non-acid GOR. In this study we only assessed acid GOR but aspiration of neutral stomach contents may be just as harmful and in dogs the vagal response to oesophageal distension is as strong as the response to acid perfusion.[36]

Even assuming that 24 hour oesophageal pH monitoring is an accurate reflection of GOR a causal link between GOR and respiratory symptoms could still be explained by postulating variation in the sensitivity of individuals to GOR. Some infants may have a highly tuned vagal reflex with an exaggerated effector response to a normal receptor stimulus. This may lead to excessive bronchoconstriction with even a normal amount of reflux. The infant whose wheeze coincided with her few episodes of GOR may exemplify this. In other infants the receptor response may be increased because of a sensitive oesophagus, either primary or secondary to oesophagitis.[37] The occasional reports of a decrease in respiratory symptoms after treatment of GOR, even when this cannot be shown to be abnormal,[13] might be explained in this way. Pharyngeal dysfunction is another possible explanation for respiratory disease caused by a normal amount of GOR and need not be severe enough to be clinically evident. While there may be more opportunity for aspiration to occur with more GOR the fate of the refluxed material when it reaches the pharynx may be more important and aspiration could occur with a single episode of reflux.

It was not possible to investigate the temporal link between GOR and respiratory symptoms in many infants as the times of more severe symptoms were not recorded. Parents were encouraged to make such recordings and discussion in most cases suggested that if changes had occurred they had been noted. It may be that the lack of such variation was because GOR was not inducing respiratory changes but it is also possible that the severity of respiratory dysfunction was such that changes were not clinically detectable. Previous studies have attempted to overcome this difficulty in demonstrating a causal role of GOR by treating it and recording the response of respiratory symptoms. Patients in such studies have shown symptomatic improvement,[4 5 7 8 11 13 14 38] but as described above these patients were usually highly selected and objective measures of respiratory function were not made.

It has been suggested that GOR may be a result of rather than a cause of respiratory symptoms with the increased pleural pressure swings associated with respiratory dysfunction provoking GOR.[39] The absence of an association between respiratory function tests results and GOR is against this being important in most infants, with the provisos already discussed. Others have suggested that increased diaphragmatic work protects against GOR by increasing lower oesophageal sphincter pressure.[40]

Some different approaches to the study of the interaction of these two common problems might be employed in future. Acidifying the infants' feeds would avoid the failure of a pH study to detect neutral reflux episodes and use of a high oesophageal pH probe might be informative, as reflux to the upper oesophagus might be more closely related to respiratory problems. Refinement of techniques for detecting microaspiration would also be helpful as radioisotope milk scans seem to be insensitive[41] and the presence of fat laden macrophages in tracheal aspirates seems to be non-specific.[42] Autonomic dysfunction may also be a fruitful area for further study as it may be a common underlying cause for both GOR and respiratory disorders[43] or GOR may cause abnormalities in autonomic function.[44]

In conclusion we have found excess GOR in a group of infants with respiratory symptoms, particularly those without a family history of atopy. However we have failed to demonstrate any association between the amount of GOR and the degree of respiratory dysfunction. Despite this there was clinical evidence of a link between the two problems in three infants and it remains possible that they are linked in more infants but that the techniques used have failed to demonstate this.

This work was supported by a grant from Janssen Pharmaceutical Limited. We would like to thank the paediatricians who referred infants under their care for investigation, the parents for agreeing to the investigations, and the parents and nursing staff for looking after the infants during the studies.

1 Mays EE. Intrinsic asthma in adults: association with gastroesophageal reflux. *JAMA* 1976;236:2626–8.
2 Mays EE, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. *Chest* 1976;69:512–5.

3 Barish CF, Wu WC, Castell DO. Respiratory complications of gastroesophageal reflux. *Arch Intern Med* 1985;**145**:1882–8.

4 Berquist WE, Rachelefsky GS, Kadden M, *et al*. Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. *Pediatrics* 1981;**68**:29–35.

5 Danus O, Casar C, Larrain A, Pope CE. Esophageal reflux—an unrecognised cause of recurrent obstructive bronchitis in children. *J Pediatr* 1976;**89**:220–4.

6 Euler AR, Byrne WJ, Ament ME, *et al*. Recurrent pulmonary disease in children: a complication of gastroesophageal reflux. *Pediatrics* 1979;**63**:47–51.

7 Jolley SG, Herbst JJ, Johnson DJ, Matlak ME, Book LS. Esophageal pH monitoring during sleep identifies children with respiratory symptoms from gastroesophageal reflux. *Gastroenterology* 1981;**80**:1501–6.

8 Jolley SG, Herbst JJ, Johnson DJ, Matlak ME, Book LS. Surgery in children with gastroesophageal reflux and respiratory symptoms. *J Pediatr* 1980;**96**:194–8.

9 Baer M, Maki M, Nurminen J, Turjanmaa V, Pukander J, Vesikari T. Esophagitis and findings of long-term esophageal pH recording in children with repeated lower respiratory tract symptoms. *J Pediatr Gastroenterol Nutr* 1986;**5**:187–90.

10 Christie DL, O'Grady LR, Mack DV. Incompetent lower esophageal sphincter and gastroesophageal reflux in acute pulmonary disease of infancy and childhood. *J Pediatr* 1978;**93**:23–7.

11 Malfroot A, Vandeplas Y, Verlinden M, Piepsz A, Dab I. Gastroesophageal reflux and unexplained chronic respiratory disease in infants and children. *Pediatr Pulmonol* 1987;**3**:208–13.

12 Shapiro GC, Christie DL. Gastroesophageal reflux and asthma. *Clin Rev Allergy* 1983;**1**:39–56.

13 Hoyoux C, Forget P, Lambrechto L. Chronic bronchopulmonary disease and gastroesophageal reflux in children. *Pediatr Pulmonol* 1985;**1**:149–53.

14 Buts JP, Barudi C, Moulin D, Claus D, Cornu G, Otte JB. Prevalence and treatment of silent gastro-oesophageal reflux in children with recurrent respiratory disorders. *Eur J Pediatr* 1986;**145**:396–400.

15 Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. *J Pediatr* 1988;**112**:847–58.

16 Martin ME, Grunstein MM, Larsen GL. The relationship of gastroesophageal reflux to nocturnal wheezing in children with asthma. *Ann Allergy* 1982;**49**:318–22.

17 Boulton TJC, Rowley MP. Incidental observations of temperament, habits and experiences of ill-health. *Aust J Paediatr* 1979;**15**:87–90.

18 Lenney W, Milner AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978;**53**:532–5.

19 Lenney W, Milner AD. Alpha and beta adrenergic stimulants in bronchiolitis and wheezy bronchitis in children under 18 months of age. *Arch Dis Child* 1978;**53**:707–9.

20 Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of oesophageal length with height: application to the Tuttle test without prior oesophageal manometry. *J Pediatr* 1979;**94**:81–4.

21 Johnson LF, Demeester TR. Development of the twenty-four hour intraoesophageal pH monitoring composite scoring system. *J Clin Gastroenterol* 1986;**8**(suppl 1):52–8.

22 Vandenplas Y, Sacre-Smits L. Continuous 24 hour pH monitoring in 285 asymptomatic infants 0–15 months old. *J Pediatr Gastroenterl Nutr* 1987;**6**:220–4.

23 Boix-Ochoa J, Lafuente JM, Gil-Vernet JM. Twenty-four hour esophageal pH monitoring in gastroesophageal reflux. *J Pediatr Surg* 1980;**15**:74–8.

24 Cucchiara S, Staiano A, Gobio Casali L, Boccieri A, Paone F. Value of the 24-hour intra-oesophageal pH-monitoring in children. *Gut* 1990;**31**:129–33.

25 Stocks J, Levy NM, Godfrey S. A new apparatus for the accurate measurement of airway resistance in infancy. *J Appl Physiol* 1977;**43**:155–9.

26 Taussig LM, Landau LI, Godfrey S, Arad I. Determinants of forced expiratory flows in newborn infants. *J Appl Physiol* 1982;**53**:1220–7.

27 Silverman M, Prendiville A, Green S. Partial expiratory flow-volume curves in infancy: technical aspects. *Bull Eur Physiopathol Respir* 1986;**22**:257–62.

28 Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for investigating thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956;**35**:322–6.

29 Stocks J, Godfrey S. Specific airways conductance in relation to post-conceptual age during infancy. *J Appl Physiol* 1977;**43**:144–54.

30 Beardsmore CS, Godfrey S, Silverman M. Forced expiratory flow volume curves in infants and young children. *Eur Respir J* 1989;**2**(suppl 4):154s–9s.

31 Vandenplas Y, Malfroot A, Dab I. Oesophageal pH monitoring criteria in infants with recurrent respiratory disease. *Pediatr Res* 1988;**24**:417.

32 Spaulding HS, Mansfield LE, Stein MR, Sellner JC, Gremillion DE. Further investigation of the association between gastroesophageal reflux and bronchoconstriction. *J Allergy Clin Immunol* 1992;**69**:516–21.

33 Wilson NM, Charette L, Thomson AH, Silverman M. Gastro-oesophageal reflux and childhood asthma: the acid test. *Thorax* 1985;**40**:592–7.

34 Herve P, Denjean A, Jian R, Simonneau G, Duroux P. Intraoesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. *Am Rev Respir Dis* 1986;**134**:986–9.

35 Mansfield L, Stein MR. Gastroesophageal reflux and asthma—a possible reflex mechanism. *Ann Allergy* 1978;**41**:224–6.

36 Mansfield L, Hameister H, Spaulding H. Smith NJ, Glab N. The role of the vagus nerve in airway narrowing caused by intraoesophageal hydrochloric acid provocation and oesophageal distension. *Ann Allergy* 1981;**47**:431–4.

37 Davis RS, Larsen GL, Grunstein MM. Respiratory response to intraoesophageal acid in asthmatic children. *J Allergy Clin Immunol* 1983;**72**:393–8.

38 Foglia RP, Fonksalrud EW, Ament ME. Gastroesophageal fundoplication for the management of chronic pulmonary disease in children. *Am J Surg* 1980;**140**:72–9.

39 Boyle JT, Tuchman DN, Altschuler SM, Nixon TE, Pack AI, Cohen S. Mechanisms for the association of gastro-oesophageal reflux and bronchospasm. *Am Rev Respir Dis* 1985;**131**:s16–20.

40 Sindel BD, Maisels MJ, Ballantine TVN. Gastro-oesophageal reflux to the proximal oesophagus in infants with bronchopulmonary dysplasia. *Am J Dis Child* 1989;**143**:1103–6.

41 Heyman S, Kirkpatrick JA, Winter HS, Treves S. An improved radionuclide method for the diagnosis of gastro-oesophageal reflux and aspiration in children (milk scan). *Radiology* 1979;**131**:479–82.

42 Staugas R, Martin AJ, Binns G, Stevens IM. The significance of fat-filled macrophages in the diagnosis of aspiration associated with gastro-oesophageal reflux. *Aust Paediatr J* 1985;**21**:275–7.

43 Chakraborty TK, Ogilvie AL, Heading RC, Ewing DJ. Abnormal cardiovascular reflexes in patients with gastro-oesophageal reflux. *Gut* 1989;**30**:46–9.

44 Axelrod FB, Maayan C, Hazzi C, Bangaru BS, Shannon DC. Bradycardia associated with hiatal hernia and gastroesophageal reflux relieved by surgery. *Am J Gastroenterol* 1987;**82**:159–61.

Archives of Disease in Childhood 1991; 66: 854–857

Vaccine efficacy and control measures in pertussis

Stephen R Palmer

Abstract

An outbreak of pertussis in primary schoolchildren in the St David's area of Pembrokeshire provided the opportunity to estimate pertussis vaccine efficacy. The estimate of efficacy was 88% when notified cases were used, but this fell to 68% when all children with bouts of coughing for two or more weeks were included. Notified cases were significantly less likely to have been vaccinated than other cases with similar symptoms. Therefore vaccine efficacy estimates based upon notified cases are likely to be biased. However, even the lower estimates suggest that pertussis immunisation is highly desirable and efforts to improve coverage should be increased.

Public anxiety about the safety and efficacy of pertussis vaccine in the United Kingdom in the 1970s led to a sharp fall in vaccine uptake and a consequent increase in the severity of pertussis epidemics in 1977/9 and 1981/3.[1] Fears about the safety of the whole cell vaccine have been addressed, but there is a continuing need to monitor vaccine efficacy, both for pertussis and other routinely administered vaccines.[2]

Measurement of vaccine efficacy requires the comparison of disease experience in vaccinated and unvaccinated children in a population in which both groups are equally exposed to the agent.[3] Outbreaks present such opportunities to carry out field evaluation of vaccine efficacy. In an outbreak of pertussis centred on a primary school in the St David's area of Pembrokeshire in 1987 vaccine efficacy was measured and the use of the accelerated schedule for vaccine delivery was evaluated.[4]

Methods

Vaccination status of all children in the study was determined from health authority records and only children with documented completed vaccination were considered to have been vaccinated for the purposes of the study. Children receiving only one or two doses of vaccine were excluded from estimates of vaccine efficacy.

Pernasal swabs were sought from notified cases, transported in charcoal media, and plated out within 12 hours on selective medium. General practitioners were asked to obtain pernasal swabs on new cases, or if that was not possible to take cough plates.

All cases of pertussis occurring in children in the two practices covering the St David's area from January 1987 to June 1987 were sought as follows. All preschool children registered in the practices were identified by the attached health visitor, families were contacted, and children who had a history of cough for two or more weeks were identified. A letter and questionnaire were sent to parents of all children in primary and secondary schools in the St Davids/Solva area on 2 June. Parents reporting illnesses in children were interviewed by the health visitor.

A *notified case* was a case formally reported by a doctor to the local authority. A *probable* case was a child with bouts of coughing lasting for two or more weeks with bouts followed by vomiting, whooping, or choking/blue colour but who was not a notified case. A *possible* case was a child with bouts of coughing for two or more weeks but without vomiting, whooping, choking or turning blue and who was not notified. Statistical comparisons were carried out by χ^2 test, *t* test, and the Mann-Whitney test.

Vaccine efficacy was estimated by three methods for a cohort of children born between 1 January 1981 and 31 December 1985 registered in the two practices and identified from the child health register.

(1) Screening method

$$PCV = \frac{PPV - (PPV \times VE)}{1 - (PPV \times VE)}$$

Where PCV=proportion of cases vaccinated, PPV=proportion of population vaccinated, and VE=vaccine efficacy.

(2) Direct population estimates

$$VE = \frac{\text{AR unvaccinated} - \text{AR vaccinated}}{\text{AR unvaccinated}}$$

Where AR=attack rate and VE=vaccine efficacy.

(3) Secondary household attack rates

Using the method of (2) above, attack rates in vaccinated and unvaccinated household contacts who were contacts of notified or probable cases were calculated. A secondary household case was a child meeting the case definition of a notified or a probable case who developed symptoms 4–30 days after a prior notified or probable case living in the same household.

Confidence intervals (CI) for estimates of vaccine efficacy were calculated through a logarithmic transformation method as described by Katz *et al*.[5]

PHLS Communicable Disease Surveillance Centre,
Welsh Unit,
Abton House,
Wedal Road,
Roath,
Cardiff CF4 3QX

Correspondence to:
Dr Palmer.

Accepted 22 March 1991

CONTROL MEASURES

The recommended schedule of childhood immunisation in Pembrokeshire was changed in June 1987 to the rapid schedule of three doses at intervals of one month starting at 3 months of age.[4] All children aged 1–7 years not having completed pertussis immunisation were identified via the child health computer register and a list sent to general practitioners and health visitors so that the children could be offered vaccination. Evaluation of the success of this policy was attempted by estimating the coverage of completed vaccination against pertussis using the child health system. A letter was sent to all general practitioners by the chief administrative medical officer on 1 June 1987 informing them of the outbreak and the changed schedule. We recommended that children suspected to have pertussis or who were contacts of known cases who developed a cough should be excluded from school for the first three weeks of illness or until they had received five days of a 10 day course of erythromycin.

Results

CLINICAL FEATURES

Forty two cases of pertussis were notified in Pembrokeshire between January and June 1987, 31 of which were from the two practices in St David's/Solva. There had been no notifications from these practices since before 1984 even though in 1986 there were 88 notifications in Pembrokeshire. *Bordetella pertussis* was isolated from one cough plate and from one of 23 pernasal swabs, although all were taken three or more weeks after onset. Additionally, 59 children in these practices met the case definition of probable cases and 44 were possible cases (table). One non-notified probable case was admitted to hospital and *B pertussis* was identified from sputum culture.

Notified cases were more likely than probable cases to have a cough followed by whooping, although when children less than 8 years of age were considered slightly more of the non-notified probable cases reported whooping (63% compared with 59%). Notified cases had a slightly longer mean duration of cough than probable and possible cases (8·5 weeks compared with 6·2 weeks, $p=0{\cdot}01$) and lost more days from school (7·4 days compared with 4·4 days, $p<0{\cdot}01$). Although the median number of bouts of coughing were the same, the mean for notified cases (3·7) was significantly greater than for the others (3·2, $p<0{\cdot}01$). Probable and possible cases were almost twice as likely as notified cases to have had a completed course of pertussis immunisation ($p<0{\cdot}05$).

VACCINE EFFICACY

(1) Screening method

In children aged 1–6 years living in Pembrokeshire five of 30 notified cases (17%) and 65·5% of the cohort were vaccinated, giving an efficacy estimate of 90% (95% CI=83 to 93%). In the two practices in the St David's area five of 24 notified cases, 11 of 22 probable cases, and nine of 17 possible cases were vaccinated. Vaccination records were missing for one probable case and two possible cases. The vaccine coverage for this cohort was 67·6%. The vaccine efficacy based upon notified cases alone, notified and probable cases, and all cases (notified, probable, and possible cases) respectively was 87% (79 to 92%), 74% (60 to 84%), and 71% (56 to 80%).

(2) Direct population estimates

In the two practices there were 175 vaccinated children aged 1–6 years of whom five were notified cases, 11 were probable cases, and nine were possible cases. Seventy three children were unvaccinated of whom 17 were notified cases, 10 were probable cases, and six were possible cases. Eleven children were incompletely vaccinated, of whom two were notified cases. Vaccine efficacy for notified cases was 88% (68 to 95%) and for notified and probable cases it was 75% (56 to 89%). When all cases were included vaccine efficacy fell to 68% (51 to 80%).

(3) Secondary household attack rates

Only 20 household contacts aged 1–6 years were identified. Ten of 17 vaccinated children had a cough for two or more weeks as did two of three unvaccinated children. The numbers were too small to calculate vaccine efficacy.

Clinical features of children with a cough for two or more weeks

	Notified cases (n=31)	*Probable cases (n=59)*	*Possible cases (n=44)*
Mean (SD) age (years)	5·4 (2·0)	7·3 (3·3)	7·7 (3·9)
No (%) who completed vaccination	7 (23)	25 (42)	21 (48)
No (%) with cough:			
Worse at night	23 (74)	44 (75)	32 (73)
Followed by:			
Vomiting	23 (74)	40 (68)	0
Whooping	19 (61)	23 (39)	0
Choking	19 (61)	33 (56)	0
Provoked by:			
Exertion	22 (71)	39 (66)	7 (16)
Eating	8 (26)	6 (10)	0
Excitement	3 (10)	5 (8)	0
Median (range) duration (weeks)	8 (3–20)	6 (2–24)	4 (2–16)
Median (range) bouts of cough/day	4 (2–4)	4 (2–5)	3 (2–4)
No with complications:			
Fits	0	1	1
Hospital admission	0	1	1
Nosebleeds	1	3	0
Otitis media	1	0	1
Median (range) days school lost (age ≥4 years)	10 (0–20)	5 (0–20)	0 (0–20)

CONTROL MEASURES

In June 1987, 66% of the cohort of children living in Pembrokeshire who were born between 29 May 1981 and 31 December 1987 were recorded as having completed pertussis immunisation. This increased to 69% in July and 70% in August. Altogether 485 children, 6·5% of the total, had received only two doses by June. This number fell to 262 in July, 209 in August, and 176 by December. Thus 65% of children who had two doses were given the third protective dose within six months of the control recommendation and 46% within one month. This group accounted for all the improvement in vaccine uptake.

Discussion

The outbreak of pertussis in the St David's area occurred in an interepidemic year. The children in this relatively isolated area appear to have escaped the outbreak in Pembroke in the previous year. Transmission seems to have occurred mainly at the end of the winter school term so that children became ill over the school holiday. On return to school transmission resumed causing a second peak of cases four weeks into the term.

Fifteen percent of children up to 15 years of age were found to have a cough for two or more weeks in the spring of 1987, and 14% of children less than 8 years of age had notified or probable pertussis. The diagnosis of pertussis was confirmed bacteriologically in only three cases but the pernasal swabs were not taken from any of the children within three weeks of onset and therefore were unlikely to have a high yield of *B pertussis*. The clinical features of children with a cough lasting two or more weeks were typical of pertussis, and 67% met our epidemiological case definition which was similar to that used in other studies.[6] The prolonged duration of illness, with a median duration of cough of 6–8 weeks, emphasises the serious nature of pertussis.

Of the 90 cases with bouts of coughing for two or more weeks followed by whooping, vomiting, or choking/turning blue only 31 were formally notified. The symptoms in the non-notified probable cases were little different from the notified cases, although duration of cough was shorter; all but six had visited their doctor. Notified cases were younger and were less likely to be vaccinated. It is possible that notified cases presented features which more clearly suggested the diagnosis of pertussis than the non-notified probable cases but in the data we collected there was no evidence of this. Almost all the children went to the same primary school and were likely to have had the same infection. An alternative explanation is that cases were less likely to be diagnosed and notified as pertussis if they were known to have been vaccinated. Such a bias would result in an overestimation of vaccine efficacy based upon notified cases only: vaccine efficacy using notified cases was 13% greater than when both notified and non-notified probable cases were used.

Another factor to be considered in interpreting these data is that estimates of pertussis vaccine efficacy will be expected to increase as the severity of disease used as a case definition increases.[1 2] There are two reasons for this: firstly, severe cases are more likely to be true pertussis and secondly, pertussis vaccine is known to reduce the severity of pertussis even when it fails to prevent disease. However, our data suggested that though notified cases had a more prolonged illness, severity as measured by frequency of coughing and complications rate was similar to that in the probable cases. The 13% difference in efficacy would appear to be the result of the notification bias.

Vaccine estimates which included possible cases (that is, without whooping, vomiting, or choking) were 5% lower than when only notified and probable cases were used. The possible cases occurred mainly in the second term and another infection may have been circulating. If so vaccine efficacy would be underestimated by including these possible cases in the calculations.

The vaccine efficacy estimate of 80% calculated by Jenkinson from cumulative data on 1–7 year olds from 1970–86 was based upon diagnostic criteria of paroxysmal cough for three or more weeks 'usually associated with vomiting and often whooping'.[7] This case definition is closer to our notified and probable cases for which we had an efficacy of 75%, with 95% confidence intervals including Jenkinson's estimate. Thus we have no evidence of a decline in efficacy for pertussis vaccine. Our data set was not large enough to examine efficacy within narrower age bands.

Routine monitoring of vaccine efficacy is highly desirable for several reasons.[1 2] The prevailing antigenic composition of the disease organism may change causing a loss of vaccine efficacy. Different commercial vaccines and even batches of the same vaccine will not have identical efficacies and monitoring may help to identify problems in production. Incorrect storage and administration as well as changes to the recommended dose, timing, frequency, and age at vaccination may be associated with reduced efficacy. Furthermore, as vaccine cover improves the proportion of cases vaccinated will increase without any fall in the efficacy. This concept is not readily appreciated and continued demonstration of efficacy will be important in maintaining confidence in the vaccine. Locally generated estimates may be more persuasive than national data in local health promotion efforts. Various methods for estimating efficacy based upon locally generated data have been proposed for local use.[8] However, our data suggest that notifications may give significantly biased estimates. Where possible cohort and case-control studies should use unbiased samples of cases identified by active case searching.

The attempts to improve uptake of the third protective dose of pertussis vaccine in children under 8 years old in Pembrokeshire were reasonably successful. About half of the children who could have benefited from a single extra dose received it within a month. No improvement in uptake among never vaccinated children was observed. The new two, three, four month schedule for pertussis vaccine introduced in

1989 in the United Kingdom now makes the accelerated schedule for outbreaks redundant.

I would like to thank Dr J Ogle, Dr SA Hamilton, Dr GW Middleton, and Dr PG Gillam for their cooperation; Miss A Ayers and Miss Sue Stevens, the health visitors, for essential assistance in carrying out this survey; and Dr Paddy Farrington, CDSC, for statistical assistance. The outbreak was managed by Dr R F Doyle, chief administrative medical officer, Pembrokeshire Health Authority with considerable support from Mr Alan James. Dr Anne Bushell, consultant microbiologist, and microbiology department staff, Withybush Hospital carried out the microbiology.

1 Begg N, Miller E. Role of epidemiology in vaccine policy. *Vaccine* 1990;8:180–9.
2 Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field, further observations. *Epidemiol Rev* 1988;**10**:212–41.
3 Orenstein WA, Bernier RH, Dondero TJ, *et al.* Field evaluation of vaccine efficacy. *Bull WHO* 1988;**63**:1055–68.
4 Joint Committee on Vaccinations and Immunizations. *Immunization against infectious disease.* London: HMSO, 1988.
5 Katz D, Baptista J, Azen SP, Pike MC. Obtaining confidence intervals for the risk ratio in cohort studies. *Biometrica* 1978;**34**:469–74.
6 Nkowane BM, Wassilak SGF, McKee PA, *et al.* Pertussis epidemic in Oklahoma. *Am J Dis Child* 1986;**140**:433–7.
7 Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from a 10 year community study. *BMJ* 1988;**296**: 612–4.
8 Clarkson JA, Fine PEM. An assessment of methods for routine local monitoring for vaccine efficacy, with particular reference to measles and pertussis. *Epidemiology and Infection* 1987;**99**:485–99.

Did Alice have glandular fever?

Here's one to test your diagnostic acumen. Did you know about the relationship between metamorphopsia and infectious mononucleosis? As you know, metamorphopsia is a form of illusion in which the form, size, movement, or colour of objects is distorted. It has been related to lesions in the occipital lobes or in the occipitotemporal or occipitoparietal regions.

In children it may be caused by infectious mononucleosis. Three children so affected were described in 1977[1] and Lahat and colleagues have recently described a 6 year old girl from Israel (*Journal of Neurology, Neurosurgery, and Psychiatry* 1990;**53**:1104). The child described the visual illusions in association with mild headache coming on two weeks after the onset of glandular fever. The episodes lasted a few minutes each time and occurred several times a day. Cranial computed tomography was normal but an EEG showed sharp high voltage waves in the parieto-occipital region. Two weeks later the EEG was normal. The symptoms lasted for four weeks.

Metamorphopsia has been called the Alice in Wonderland syndrome.[2] Apparently it can come on before, with, or after the other features of glandular fever.

ARCHIVIST

1 Copperman SM. 'Alice in wonderland' syndrome as a presenting symptom of infectious mononucleosis in children: a description of three affected young people. *Clin Pediatr (Phila)* 1977;**16**:143–6.
2 Todd J. The syndrome of 'Alice in wonderland'. *Can Med Assoc J* 1955;**73**:701–4.

Archives of Disease in Childhood 1991; 66: 858–861

Acquired aplastic anaemia: still a serious disease

D K H Webb, I M Hann, J M Chessells

Abstract

Over 15 years, 42 children aged 2–14 years were diagnosed as having acquired aplastic anaemia. Adequate clinical details were available for 38 children who were categorised as very severe (n=13), severe (n=16), or non-severe (n=9) by the modified Camitta criteria.

Treatment varied over the study period. Seven children received a bone marrow allograft from a full match family donor and three a matched unrelated donor transplant after failed treatment with antilymphocyte globulin. The remainder were treated with antilymphocyte globulin (n=11), antilymphocyte globulin and oxymetholone (n=4), oxymetholone with or without prednisolone (n=12), or supportive treatment alone (n=1).

With a minimum follow up of one year since treatment, the five year survival was 70% for bone marrow transplantation with a family donor, 30% for antilymphocyte globulin, and 25% for oxymetholone. All three children with a matched unrelated donor transplant died.

The prognosis of acquired aplastic anaemia remains poor for most children and new approaches to treatment are urgently required.

Aplastic anaemia is a rare but often fatal disorder of haemopoiesis. It is characterised by blood pancytopenia and bone marrow hypoplasia and affected 2–4 per million children under 15 years in one Danish series.[1] The incidence is higher in the Orient,[2] probably reflecting increased exposure to environmental toxins and hepatitis.[3] The bone marrow failure may be constitutional or acquired: constitutional causes include Fanconi's anaemia, dyskeratosis congenita, and Shwachman's syndrome. Although drugs, toxins, and viruses have been implicated in the aetiology of acquired aplastic anaemia, over 70% of cases are idiopathic.[4] There is conflicting evidence that in some cases acquired aplastic anaemia is an immune mediated disorder,[5 6] and 50% of patients show an improvement with immune suppression.[7] Only 20% of severely affected children survive one year from diagnosis with supportive care alone,[8] and although allogeneic bone marrow transplantation may be curative, only 30% of patients have a suitable family donor. There are few paediatric data, and the outcome for children treated over a 15 year period at a single institution is presented.

Patients and methods

Over the 15 year period, January 1974 to December 1988, 42 children were diagnosed as having acquired aplastic anaemia at the Hospital for Sick Children, Great Ormond Street, London. The medical records were reviewed for details of age, sex, case history, laboratory investigations, aetiology, and outcome. Adequate details were available for 38 children (17 boys, 21 girls) with a median age of 6 years (range 2–14) at diagnosis.

Laboratory investigations included the acidified serum lysis (Ham's) test for paroxysmal nocturnal haemoglobinuria, cytogenetic analysis of blood lymphocytes stressed with diepoxybutane or mitomycin C for Fanconi's anaemia, virology, liver function tests, and a trephine biopsy to assess accurately marrow cellularity. Severity was assessed by the modified Camitta criteria.[9] Children with severe aplastic anaemia had a pancytopenia with at least two of the following features: neutrophil count $<0{\cdot}5\times10^9$/l, platelet count $<20\times10^9$/l, corrected reticulocyte count<1%, and a bone marrow trephine with residual haemopoietic cells <30% of normal cellularity. Children with very severe aplastic anaemia fulfilled these criteria, but had a neutrophil count of $<0{\cdot}2\times10^9$/l, whereas more mildly affected individuals had non-severe aplastic anaemia.

Treatment varied over the study period but all children received broad spectrum antibiotics, antifungal therapy, and blood and platelet transfusions as clinically indicated. Families were tissue typed soon after diagnosis. Children with severe or very severe aplastic anaemia and an HLA full match family doctor were treated by allogeneic bone marrow transplantation, either at Great Ormond Street, the Royal Marsden, or Hammersmith Hospitals. Pretransplant conditioning was with cyclophosphamide in each case, and graft versus host disease prophylaxis was by methotrexate (n=5), cyclosporin (n=4), or T cell depletion (n=1). Before 1980 children without a bone marrow donor, or with non-severe disease, were treated by oral oxymetholone 2·5 mg/kg/day usually combined with prednisolone. Since 1980 these children received horse antilymphocyte globulin (ALG, Merieux) 1·5 vials/10 kg/day for five days by a central venous catheter, with prophylaxis of serum sickness by methylprednisolone 5mg/kg/day. Children treated with supplementary androgens received oxymetholone 2·5 mg/kg/day for four months after completion of antilymphocyte globulin. If there was an inadequate response to horse antilymphocyte globulin by four months after treatment patients received a five day course of rabbit antilymphocyte globulin.

The Department of Haematology and Oncology, The Hospital for Sick Children, London
D K H Webb
I M Hann
J M Chessells

Correspondence to:
Dr D K H Webb,
Department of Paediatrics,
Llandough Hospital,
Penarth,
South Glamorgan CF6 1XX.

Accepted 28 February 1991

[redacted]

transplant was not significant on Kaplan-Meier analysis (p=0·08).

Discussion

Acquired aplastic anaemia remains a rare but severe disease in childhood. Most cases are idiopathic—in this series only three of 34 children had a possible causative agent, each being infective—and review of the literature indicates that drug or toxin induced aplasia and paroxysmal nocturnal haemoglobinuria are rare among Western children. A higher incidence of aplastic anaemia due to drug toxicity and hepatitis has been described in the Orient.[2 3] The mechanism of bone marrow failure is unclear, although there is conflicting evidence from culture experiments for an immune mediated suppression of haemopoiesis. There have been reports of 40–70% of children[8 10 11] and 50–60% of adults[7] showing an improvement after immune suppressive treatment with antilymphocyte globulin, although blood values return to normal in only a minority of cases. In several series up to 50% of adults treated with antilymphocyte globulin have subsequently developed a clonal disorder of haemopoiesis including acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria, or myelodysplasia.[12 13] This argues for an underlying defect of haemopoiesis in many cases. These complications have not been described in children, however, and it is possible that a different mechanism of bone marrow failure operates in childhood. Despite a male preponderance in the adult series, there was no sex difference in incidence in this study.

In this series 29 of 38 children had severe or very severe aplastic anaemia. An increased severity of aplastic anaemia in childhood has been described,[14] although the small number of paediatric cases precludes definite conclusions on relative severity. Haemorrhage or sepsis at diagnosis is associated with a poor prognosis,[15] and in our report five of six children with bleeding at presentation died.

Allogeneic bone marrow transplantation from an HLA full match family donor is the treatment of choice for severe and very severe aplastic anaemia, and in our series five of seven children are alive in full health; this is consistent with other reports.[8 11 16 17] It is important that all families are tissue typed soon after diagnosis, and children with a donor and severe or very severe aplastic anaemia should be treated by early transplantation. Bone marrow transplantation from a matched unrelated donor or a family donor with minor mismatch has been successful in some cases.[18 19] Although three children with a matched unrelated donor in this series died, all were late transplants in pretreated patients with a high risk of treatment failure.[20] Our present policy is to initiate a matched unrelated donor search for all severely affected children without a suitable family donor soon after diagnosis as the published results of matched unrelated donor transplants are more promising than the outcome with other second line treatment. Preparative regimens influence survival and there have been poor results in patients treated by schedules including methotrexate. The combination of cyclophosphamide with cyclosporin carries a low risk of graft rejection (17%)[21] and graft versus host disease, although the incidence of long term sequelae such as infertility and secondary malignancies is unclear.

The survival after treatment with oxymetholone alone was poor, consistent with other series,[15] and no better than that obtained with supportive care.[14] Antilymphocyte globulin was of only limited benefit in this series, with no evidence of a survival advantage compared with androgen treatment. Only five of 18 children showed a complete response and patients with a partial response had a high relapse rate. These data are consistent with the 40–50% five year survival reported for children with severe aplastic anaemia receiving antilymphocyte globulin in four paediatric series.[8 11 17 20] Werner *et al* described a 70% response rate but numbers were small and survival data limited in their series.[10] A higher response and survival rate has been described in predominantly adult patients with non-severe aplastic anaemia,[7] and a poor outcome is predicted by young age, female sex, neutrophil count $<0{\cdot}2\times10^9$/l, and bleeding or sepsis at diagnosis.[15] The approach to treatment for a child with non-severe aplastic anaemia and an HLA full match family donor is controversial. It is probably best managed by a trial of antilymphocyte globulin in the first instance and with bone marrow transplantation reserved for children with other, poor prognostic features, or who have less than a complete response to antilymphocyte globulin.

For children who fail first line treatment responses have been described after immune suppression by cyclosporin or high doses of methylprednisolone.[22 23] Of these cyclosporin is the more promising with a 30% response rate in patients who relapse after or fail to respond to antilymphocyte globulin, and in our series one child has shown steady improvement without toxicity. Treatment with recombinant granulocyte macrophage colony stimulating factor is effective in raising the neutrophil count in aplastic anaemia, but had no effect in patients with very low neutrophil counts or sepsis at the time of treatment,[24] and it is essentially supportive therapy.

Despite advances in treatment the prognosis of aplastic anaemia remains poor in a large proportion of cases. New approaches to treatment are required to reduce the morbidity and mortality associated with this disease.

We wish to thank Dr JM Hows, Professor EC Gordon-Smith, the late Professor TS McElwain, and Dr Ray Powles for their help in the management of these patients, and Miss Sonia Taylor who typed this manuscript.

1 Clausen N. A population study of severe aplastic anaemia in children. *Acta Paediatr Scand* 1986;75:58–63.
2 Young NS, Issara Grasil S, Chick CW, Takaku F. Aplastic anaemia in the Orient. *Br J Haematol* 1986;62:1–6.
3 Liang DC, Lin KH, Lin DT, Yang CP, Hung KL, Lin KS. Post-hepatitic aplastic anaemia in children in Taiwan, a hepatitis prevalent area. *Br J Haematol* 1990;74:487–91.
4 Alter BP, Potter NU, Li FP. Classification of the aplastic anaemias. *Clin Haematol* 1978;7:431–65.
5 Hoffman R, Zanjani ED, Lutton JD. Suppression of erythroid colony formation by lymphocytes from patients with aplastic anemia. *N Engl J Med* 1977;296:10–3.
6 Sullivan R, Quesenberry PJ, Parkman R, *et al*. Aplastic anemia: lack of inhibitory effect of bone marrow lymphocytes on in vitro granulopoiesis. *Blood* 1980;56:625–32.
7 Marsh JCW, Hows JM, Bryett KA, *et al*. Survival after anti-

lymphocyte globulin therapy for aplastic anemia depends on disease severity. *Blood* 1987;**70**:1046–52.

8 Halpérin DS, Grisaru D, Freedman MH, Saunders EF. Severe acquired aplastic anemia in children: 11 year experience with bone marrow transplantation and immunosuppressive therapy. *Am J Pediatr Hematol Oncol* 1989;**11**: 304–9.

9 Camitta B, O'Reilly RJ, Sensenbrenner L, *et al.* Antithoracic duct lymphocyte globulin therapy of severe aplastic anemia. *Blood* 1983;**62**:883–5.

10 Werner EJ, Stout RD, Valdez LP, Harris RE. Immunosuppressive therapy versus bone marrow transplantation for children with aplastic anemia. *Pediatrics* 1989;**83**:61–4.

11 Locasciulli A, Van't Veer L, Bacigalupo A, *et al.* Treatment with marrow transplantation or immunosuppression of childhood acquired severe aplastic anaemia: a report from the EBMT SAA Working Party. *Bone Marrow Transplantation* 1990;**6**:211–7.

12 Tichelli A, Greatcooke A, Wursch A, *et al.* Late haematological complications in severe aplastic anaemia. *Br J Haematol* 1988;**69**:413–8.

13 De Planque MM, Kluin-Nelemans HC, Van Krieken HJM, *et al.* Evolution of acquired severe aplastic anaemia to myelodysplasia and subsequent leukaemia in adults. *Br J Haematol* 1988;**70**:55–62.

14 Najean Y, Girot R, Baumelou E. Prognostic factors and evolution of acquired aplastic anemia in childhood. *Am J Pediatr Hematol Oncol* 1984;**4**:273–83.

15 Bacigalupo A. Treatment of severe aplastic anaemia. In: Gordon-Smith EC, ed. *Clinical haematology*. London: Baillière Tindall, 1989.

16 McGlare PB, Haake R, Miller W, Kim T, Kersey J, Ramsey NK. Therapy of severe aplastic anemia in young adults and children with allogeneic bone marrow transplantation. *Blood* 1987;**70**:1325–30.

17 Bayerer E, Champlin R, Ho W, *et al.* Comparison between bone marrow transplantation and antilymphocyte globulin in the treatment of young patients with severe aplastic anemia. *J Pediatr* 1984;**105**:920–5.

18 Bacigalupo A, Hows JM, Gordon-Smith EC, *et al.* Bone marrow transplantation for severe aplastic anaemia from donors other than HLA identical siblings: a report of the BMT Working Party. *Bone Marrow Transplantation* 1988;**3**: 531.

19 Hows JM, Yin JL, Marsh JCW, *et al.* Histocompatible unrelated volunteer donors compared with HLA nonidentical donors in marrow transplantation for aplastic anemia and leukemia. *Blood* 1986;**68**:1322.

20 Locasciulli A, Porta F, Vossen JM, Bacigalupo A. Treatment of acquired severe aplastic anaemia (SAA) in children: an analysis of the EBMT–SAA Working Party. *Bone Marrow Transplantation* 1989;**4**(suppl 2):90.

21 Hows JM, Gluckman E, Devergie A, Bacigalupo E. The effect of conditioning protocols on outcome of BMT for severe aplastic acquired anaemia. *Bone Marrow Transplantation* 1989;**4**(suppl 2):92.

22 Leonard EM, Raefsky E, Griffith P, *et al.* Cyclosporin therapy in aplastic anaemia, congenital and acquired red cell aplasia. *Br J Haematol* 1989;**72**:278–84.

23 Ozsöylu S, Coskun T, Minassezi S. High dose intravenous glucocorticoids in the treatment of childhood acquired aplastic anaemia. *Scand J Haematol* 1984;**33**:309–16.

24 Raghavachar A, Frickhofen N, Kaltwasser JP, *et al.* GM-CSF therapy in aplastic anaemia patients with very severe neutropenia. *Bone Marrow Transplantation* 1990;**5**(suppl 2): 36.

Autoantibodies in juvenile chronic arthritis

Autoantibodies against nuclear and other antigens are found in patients with juvenile chronic arthritis. In diseases such as systemic lupus erythematosus and progressive systemic sclerosis family members frequently also have autoantibodies but this aspect has not been investigated as regards juvenile chronic arthritis until now. Such a study has recently been reported from Australia (Southwood *et al*, *Annals of the Rheumatic Diseases* 1990; **49**:968–72).

They investigated 23 children with the disease and 66 of their first degree relatives. Antinuclear antibodies were found in 16 patients (70%) and nine relatives (14%). In Australia 3·5% of the general population are thought to have such antibodies. Eighteen out of 20 families had at least one member with autoantibodies in addition to the one with juvenile chronic arthritis. Immunoblotting showed patterns shared between probands and other members in five families.

This study confirms that antinuclear antibodies are common in juvenile chronic arthritis and shows that apparently unaffected family members may also have these antibodies. It seems likely that there is a genetically determined tendency to produce autoantibodies in this as in other autoimmune diseases.

ARCHIVIST

Archives of Disease in Childhood 1991; **66**: 862–865

Referrals to child psychiatry—a survey of staff attitudes

S Oke, R Mayer

Abstract

A questionnaire study was conducted in a health district to evaluate the attitudes of paediatricians and child psychiatry staff as to which categories of problems should be referred to child psychiatry. In the majority of categories the two groups disagreed as to the frequency with which the problem should be referred. In the categories relating to child sexual abuse responses were often not in accord with Department of Health and Social Security guidelines. Reasons for not referring were also looked at and again it was found that there were a number of significant differences in opinion as to what are reasons for not referring to child psychiatry. Both groups agree that lack of communication is a reason for non-referral. Some suggestions are made as to how this problem could be addressed.

The association between child psychiatry and paediatrics has been widely commented on during the past 30 years.[1–5] We wished to explore whether locally there was agreement between disciplines as to the appropriateness of referral of various clinical problems and to look at factors that might lead to not referring.

Method

The study was a survey, using specially designed questionnaires, of paediatricians (all grades) and child psychiatry staff (psychiatrists, clinical psychologists, child psychotherapists, and social workers) in an inner London health district. The decision to survey only medical staff in paediatrics but all professional child psychiatry staff reflects the fact that whereas referral, although influenced or initiated by other professions, is primarily a medical decision, the child psychiatry departments assess and treat on multidisciplinary lines.

THE QUESTIONNAIRES

Two questionnaires were used, one for paediatricians and one for child psychiatry staff. They varied slightly in format, but were identical in content. Both questionnaires consisted of two parts.

Part 1

The aim of part 1 was to determine whether paediatricians and child psychiatrists agree as to which type of clinical problem should be referred to child psychiatry. Part 1 of the paediatricians' questionnaire asked paediatricians how often they would refer to child psychiatry a range of clinical problems seen as inpatients and outpatients. Part 1 of the child psychiatry questionnaires asked child psychiatry staff how often they think paediatricians should refer these problems to the child psychiatry department.

The clinical problems were selected for inclusion after a review of the literature[6–8] and after discussions with our colleagues. Our list was not exhaustive but represented most of the common reasons for referral to child psychiatry.

Respondents were asked to indicate how frequently they felt a category of problem should be referred by answering 1–4 where 1=rarely or never, 2=sometimes, 3=frequently, and 4=always or nearly always. The categories of problems are shown in table 1.

Part 2

This section looked at factors that might negatively influence referral. The list of possible reasons we used was compiled after a review of the literature and after discussions with our colleagues. These possible reasons were given in the form of a list of statements and the respondents were asked to indicate 'yes' or 'no' to each of these depending on whether or not they thought the reason relevant in the decision not to refer to child psychiatry. These statements are shown in table 2.

In this part of the questionnaire we were asking paediatricians direct attitudinal questions, but the child psychiatry staff were being asked to speculate whether they felt certain factors affected the paediatricians' decision to refer. Both parts of the questionnaires included a section inviting further comments from the respondents. Questionnaires were sent to all the staff indicated above with an explanatory letter and prepaid reply envelopes. A reminder and a second copy of the questionnaire were sent if there was no response within three weeks. We indicated that respondents could reply anonymously if preferred.

Results

RESPONSE RATES

The response rate to the questionnaires was 23/37 (67·6%) for paediatricians and 25/37 (67·6%) for child psychiatry staff.

We originally recorded the results by subgrouping the respondents according to department (paediatrics or child psychiatry), hospital or centre and either status, if paediatric, or discipline, if child psychiatric (for example, senior

St Mary's Hospital and Paddington Green Department of Child Psychiatry, London
S Oke
R Mayer

Correspondence to:
Dr S Oke,
Wonford House Hospital,
Dryden Road,
Wonford,
Exeter EX2 5AF.

Accepted 28 February 1991

Table 1 Results to part 1 of the questionnaire: which type of clinical problem should be referred to child psychiatry

Category of problem	*Department**	*Respondents (%) who refer:*				*Total No of responses*	*Significance*
		Always	*Frequently*	*Sometimes*	*Never*		
(A) Self poisoning	P	71	24	0	5	21	NS
	CP	88	8	4	0	25	
(B) Emotional/ behavioural problems	P	4·5	32	54·5	9	22	p<0·01
	CP	56	28	11	7	25	
(C) Obesity	P	0	0	55	45	22	p<0·01
	CP	12	24	60	4	25	
(D) Helping families/children cope with terminal illness	P	22	13	38	17	22	NS
	CP	8	48	40	4	25	
(E) Helping famillies/children cope with physical handicap/chronic illness	P	0	17	61	22	23	NS
	CP	0	16	80	4	25	
(F) Repeated admissions (because mother cannot cope)	P	0	22	48	30	23	NS
	CP	20	8	64	8	25	
(G) Physical illness exacerbated by psychological problems	P	4	26	52	17	23	p<0·01
	CP	20	48	8	0	25	
(H) Diagnostic difficulties	P	16	36	40	8	25	p<0·01
	CP	53	22	20	5	22	
(I) Child sexual abuse+behavioural/ emotional problems	P	53	19	19	9	21	p<0·01
	CP	88	8	4	0	25	
(J) Help with diagnosing child sexual abuse	P	27	27	14	32	22	p<0·01
	CP	44	36	16	4	25	
(K) Encopresis	P	17	39	31	13	23	NS
	CP	16	64	20	0	25	
(L) Enuresis	P	0	0	47	53	23	p<0·01
	CP	12	60	28	0	25	
(M) Admission problems/ separation anxiety	P	0	19	48	33	21	p<0·01
	CP	20	40	28	12	25	
(N) Parental neglect/ non-accidental injury	P	4	13	48	35	23	p<0·01
	CP	32	28	40	0	25	
(O) Drug/alcohol problems in child	P	32	55	13	0	22	NS
	CP	44	40	16	0	25	
(P) Anxiety over medical/ nursing procedures	P	0	5	43	52	21	p<0·01
	CP	8	20	52	20	25	
(Q) Behaviour disturbance on ward	P	14	24	52	10	21	p<0·01
	CP	50	33	17	0	25	
(R) Mother has difficulties with baby feeding/sleeping	P	4	13	48	35	23	p<0·01
	CP	36	28	36	0	25	
(S) Don't know what else to do	P	4	4	57	8	23	p<0·01
	CP	24	16	44	16	25	

*P=paediatrics, CP=child psychiatry.

Table 2 Results to part 2 of the questionnaire: factors that might negatively influence referral

(1) Referral not acceptable	P	100	0	22	NS
	CP	100	0	25	
(2) Stigmatises child or family	P	14	86	22	P<0·01
	CP	75	25	24	
(3) Delay before first appointment too long	P	45·5	55·5	22	P<0·01
	CP	52	48	25	
(4) Delay before treatment too long	P	41	59	22	NS
	CP	50	50	24	
(5) Treatment range narrow/inappropriate	P	50	50	22	P<0·01
	CP	68	32	25	
(6) Psychiatric process damages child	P	5	95	21	P<0·01
	CP	41	59	22	
(7) Lack of child psychiatry inpatient/ day patient facility	P	48	52	21	NS
	CP	65	35	23	
(8) Inadequate communication between departments	P	77	23	22	NS
	CP	24	16	25	
(9) Case is 'lost' to child psychiatry after referral	P	40	60	22	NS
	CP	62·5	37·5	24	
(10) Medical opinion sought†	P	41	59	22	NS
	CP	52	48	25	
(11) Opinion of consultant psychiatrist sought but difficult to obtain	P	27	73	22	NS
	CP	56	44	25	
(12) If all cases referred child psychiatry system would be flooded	P	32	68	22	NS
	CP	36	64	25	
(13) Referral does not achieve much	P	48	52	21	NS
	CP	72	28	25	

*P=paediatrics, CP=child psychiatry.
†A medical opinion sought but child frequently seen by non-medical child psychiatry staff.

house officer or psychologist). However, there were no superficial differences between these subgroups within each department and the numbers in some of the subgroups were very small and therefore the responses were pooled according to department for analysis.

Part 1

Results are given in table 1. The percentage of paediatricians and child psychiatry staff responding with either 1, 2, 3, or 4 to each category of problem A to S is given. The total number of responses to each category is also given. These totals vary as a number of questionnaires were only partially completed. The results were analysed using non-parametric correlation coefficient Kendall's τ for tied ranks to see if there was a significant difference between the responses of the paediatricians and the child psychiatric staff.[9] The rationale for using this method is discussed by Priest.[10] The result of this analysis is given in table 1.

There was a significant difference in the responses to 13 out of 19 categories. Particularly striking disagreement was seen in the categories of obesity, enuresis, and 'behavioural problems referred directly to the paediatrician'. When there was a difference in responses it was always that the child psychiatry staff indicated that the case should be referred and the paediatricians indicated that it should not.

There was agreement between the two groups' responses to four of the categories. Firstly, both paediatricians and child psychiatry staff agreed that category A (self poisoning) and O (drug and alcohol problems) should be referred to child psychiatry. Both groups also agreed that categories E (helping families and children cope with physical handicap or chronic illness) and F (children with repeated admissions because the mother cannot cope) should not be referred to child psychiatry.

Part 2

We recorded the percentage of 'yes' and 'no' responses given by both groups of staff to each of the statements 1 to 13. The results are given in table 2. Again, some of the questionnaires were incomplete and so the total number of responses varied. These results were analysed using the χ^2 test with Yates's correction for continuity. Significant differences were found in the responses to two of the statements. To statement 2 (referral stigmatises the child or family) paediatricians indicated that this was not a reason for not referring whereas child psychiatry staff thought this was a reason for not referring. Paediatricians responded to statement 6 (the psychiatric process damages the child) by indicating that this was not a reason for not referring whereas child psychiatry staff were divided in their responses to this statement.

Both groups agreed that statements 1 (referral not acceptable to the family) and 8 (inadequate communication between the departments after the child is seen) are reasons for not referring. Both groups also agree that statement 12 (if all appropriate cases were referred the child psychiatry department would be flooded) was not a reason for not referring.

COMMENTS

Some of the comments made in response to the question posed at the end of part 2 of the questionnaires: 'Do you think there are any other reasons for not referring to the child psychiatric department' are given below. The asterisked comments were made by anonymous respondents.

Comments from paediatricians

- 'Psychiatrists seem aloof from everyday problems that families face and from problems on the ward'.

[redacted]

- 'There is a cultural gap between the local population and the staff of the child psychiatry clinics—more medical approach and perhaps more work with other professionls in the community might be more helpful'.
- 'Reluctance on the part of the child psychiatrist to see the patient'.
- 'Child psychiatry should be part of the range of services provided by paediatrics and not a separate department to whom referrals are made'.
- 'A child psychiatrist is not present on site as part of the paediatric team'.
- 'I feel that both paediatricians and child psychiatric trainees should spend six months in each other's professions in order to better understand the job'.
- 'Heavy demand on parents with frequent (two to three times a week) therapy sessions'.*
- 'General requirement that both parents should be prepared to go to the initial appointment'.*
- 'Low profile of psychiatric department within paediatric department—but improving'.

Comments from child psychiatry staff

- 'Paediatricians sometimes think they can offer the same help as child psychiatry would give'.
- 'Resistance to conceptual basis of child psychiatry/psychotherapy'.
- 'Some paediatricians (not all) may find it hard to accept that they are not experts in all aspects of illness in children. . . . in the good old days paediatricians did have to cope with all aspects of childhood illness, including psychological aspects. Lack of child psychiatric resources in some areas may mean that paediatricians are still dealing with what should ideally be dealt with by child psychiatrists'.
- 'Paediatricians' own anxieties about (a) emotions being stirred up, (b) working with other professionals, (c) losing control of the situation'.
- 'The department is seen as too narrow in its range of work and intransigent'.
- 'Ignorance and lack of communication between the two departments'.

There were no comments made in response to part 1 of the questionnaire.

Discussion

The response rate was 67·6% for both paediatricians and child psychiatry staff. Some of the junior paediatric staff gave the reason that they member of the child psychiatry department to see the child and/or family.

Part 1 of the questionnaire

There was agreement between paediatricians and child psychiatric staff on only a few categories of problems and significant disagreement was seen in the responses of the two groups to most of the categories. In cases of child sexual abuse with emotional or behavioural disturbance 72% of paediatricians and 96% of child psychiatry staff said they would always or frequently refer. This difference is significant and contradicts Department of Health and Social Security (DHSS) guidelines that recommend referral to child psychiatry.[11] Interestingly, 80% of child psychiatry staff and 54% of paediatricians favoured always or frequently referring cases requiring help with the diagnosis of child sexual abuse. This difference is significant and again contradicts DHSS guidelines, which advise that such cases should not be referred to child psychiatry.[11]

It was noted that when there was a significant difference between child psychiatry staff and paediatricians it was always that the child psychiatrists were in favour of referral and paediatricians were against it. One possible explanation of these findings is that paediatricians and child psychiatrists may have different ideas about these problems. It is likely that paediatricians would see a broad range in severity of these cases but the child psychiatric staff may only see the more severe cases. Another possible cause of these differences may be the apparent lack of communication between the two departments. This idea is supported by the results of part 2 of the questionnaire and by some of the comments made by the respondents.

Part 2 of the questionnaire

This part looked at reasons for not referring to child psychiatry. Unfortunately, it is not clear whether responding 'no' in this part of the questionnaire indicates that the respondent thinks that the statement is incorrect or that the statement is correct but not relevant in influencing non-referral. The questionnaire has compounded these two distinct questions and a further study is needed to overcome this problem. Some interesting results were seen in the responses to statement 5 ('range of treatment too narrow or inappropriate') and statement 13 ('referral to child psychiatry does not seem to achieve much'). A large number of child psychiatry staff responded 'yes' to both statements. This could mean that either this group is dissatisfied with their work or that they feel that they are poorly perceived by their paediatric colleagues. The comments received from the paediatricians supports the second conclusion.

Both departments agreed that inadequate communication was a reason for non-referral. The agreement on this issue is striking and is reflected in some of the respondents' comments. It is suggested that this may be underlying some of the differences found in part one of the study.

This could be readily addressed by more active attempts at communication between the two groups. Joint ward rounds or clinical meetings could be a suitable forum in which this could take place. If all the cases that the child psychiatry staff suggest were referred it would undoubtedly result in a flooding of the service. More consultative work and mutual education could take place in such meetings thereby reducing the perceived need for many of these referrals. Also, perhaps a jointly formulated referral policy could be initiated.

The authors wish to thank Dr IT Dresser, Professor TE Oppe, and Professor RG Priest for their advice and the paediatric and child psychiatry staff for their help and participation in the study.

1 Eisenberg L. The relationship between psychiatry and pediatrics: a disputatious view. *Pediatrics* 1967;**39**:645–7.
2 Anders TF. Child psychiatry and pediatrics—the state of the relationship. *Pediatrics* 1977;**60**:616–20.
3 Jellinek MS. The present status of child psychiatry in pediatrics. *N Engl J Med* 1982;**306**:1227–9.
4 Taylor DC. Child psychiatry/paediatric liaison: a discussion paper. *J R Soc Med* 1986;**79**:726–8.
5 Fritz CK, Bergman AS. Child psychiatrists characteristics as described by pediatricians in a national survey (1986–1987). *Int J Psychiatry Med* 1986;**16**:91–100.
6 Mrazek D. Child psychiatric consultation and liaison to paediatrics. In: Rutter M, Hersov L, eds. *Child and adolescent psychiatry—modern approaches.* 2nd Ed. Oxford: Blackwell Scientific, 1976.
7 Lewis M. Child psychiatric consultations in pediatrics. *Pediatrics* 1978;**62**:359–64.
8 Monnelly EP, Lanzito BM, Stewart MA. Psychiatric consultations in a children's hospital. *Am J Psychiatry* 1973;**130**: 789–90.
9 Kendall MG. *Rank correlation methods.* 3rd Ed. London: Griffin, 1962.
10 Priest RG. The homeless person and the psychiatric services: an Edinburgh survey. *Br J Psychiatry* 1976;**128**:128–36.
11 Department of Health and Social Security. *Diagnosis of sexual abuse: guidance for doctors.* London: HMSO, 1988.

Archives of Disease in Childhood 1991; **66:** 866–869

Children with pervasive refusal

B Lask, C Britten, L Kroll, J Magagna, M Tranter

Abstract

Four children are described with a potentially life threatening condition manifested by profound and pervasive refusal to eat, drink, walk, talk, or care for themselves in any way over a period of several months. The multiplicity and severity of the symptoms in these children do not fit comfortably into any existing diagnostic category. Long term and highly skilled nursing and psychiatric care is required to help these children to recover. The possible causes of this syndrome are discussed.

Child psychiatric disorders may vary from relatively mild, albeit distressing symptoms such as enuresis, encopresis, behaviour problems or school refusal, through to the devastating effects of psychotic illness or life threatening problems such as anorexia nervosa or severe depression with suicidal ideology and intent. We have recently seen a number of children with a profound and pervasive life threatening condition manifested by dramatic social withdrawal and determined refusal to walk, talk, eat, drink, or care for themselves in any way for several months. Careful history taking and physical examination and investigation at the time of presentation excluded any organic disease.

Case reports

CASE 1

A girl, aged 13, was transferred from a paediatric ward to our child psychiatric unit with a four month history of increasing pain and stiffness in her right leg, leading eventually to an apparent inability to walk. As her mobility diminished she reported that she could no longer see or swallow, and over the next few weeks she stopped speaking and lost the use of all four limbs. She refused, by screaming and vigorous physical endeavour, all attempts to assist her. Thus attempts at oral feeding led to her tightly closing her mouth, turning away her head, and spitting out any food or drink. There was no sleep disturbance. The only abnormality on physical examination was a finger sized hole in the hymen and abrasion of the right labium, with some vaginal discharge.

The girl's physical and intellectual development had been normal, but aged 4 she had been reported to be 'aggressive', and her premorbid personality was described as 'like an old lady, lacking childishness and fun'. She had a sister 10 years older than her, and her parents who were in their 50s had both previously been treated for depression.

Despite intensive attempts to rehabilitate her she continued to deteriorate. She required nasogastric feeding and, on two occasions, manipulation of her joints under general anaesthetic to prevent contractures. The nursing care she required was that necessary for a patient with quadriplegia. She continued to resist all attempts to help her. Individual and family therapy shed little light on the cause of her illness, although an overinvolved and covertly sexual relationship between the girl and her father was noted. Further investigation and exploration of this was unproductive.

After six months she slowly started to improve and one year after admission she could walk with minimal assistance, could obviously see although denying it, and could when necessary make herself heard. At this point she was transferred to the Bethlem Royal Hospital Adolescent Unit, with the expectation that she would require long term care. As her physical state continued very slowly to improve, her behaviour changed. She became far more outgoing, incited others to misbehave, stimulated interest in seances and black magic, and teased maliciously about sexual matters. On a number of occasions she ran away. She was finally discharged from hospital three years after her original admission and at three year follow up had remained well.

CASE 2

A girl, aged 11, was transferred to our unit from a paediatric ward with a one year history of panic attacks and prolonged episodes of screaming. For three months she had refused to eat, drink, walk, or take care of herself. She angrily refused to answer questions, described herself as very sad, and expressed a wish to die. Under no circumstances did she wish to go home. She resisted help with angry screams and at times physical aggression.

She was the second of three children and her physical and intellectual development had been normal. Her premorbid personality was described as 'anxious and perfectionistic'. Early separation problems had been noted, and at aged 7 there had been reports of 'sexually provocative behaviour'. There was no family history of significance.

The first three months of her admission were stormy with continuing and determined refusal to eat, drink, walk, or care for herself. She continued to scream whenever anyone communicated with her. Treatment consisted of a com-

Hospital for Sick Children, Great Ormond Street, London WC1N 3JH
B Lask
C Britten
L Kroll
J Magagna
M Tranter

Correspondence to:
Dr Lask.

Accepted 3 March 1991

bination of individual, group, and family therapy, and the use of the ward milieu. In individual interviews she eventually admitted to having a secret, and further painstaking exploration led to disclosure of prolonged and repeated sexual abuse, including the use of physical restraint and punishment. She refused to name the perpetrator(s). After the disclosure and further discussion of her experiences she slowly started to improve. She remained unable to allow a full physical examination but gradually became calmer and resumed eating, drinking, and walking.

She suffered a transient relapse during Christmas leave when she claimed to have seen the perpetrator. Subsequently she was made a ward of court and her parents were allowed only supervised access. Nine months after admission and 21 months from the onset of the illness she

depressive content. Her self care and hygiene improved and she permitted touching, but for several more weeks retained her hunched, withdrawn posture and refused to speak. Approximately one year after admission she adopted a more upright posture, started talking, and ate and drank normal portions. Family and individual therapy focused on fears of violence, and although possible physical, emotional, and sexual abuse were investigated, none was elicited. She remained silent throughout these interviews. She was discharged, on no medication, to residential schooling 18 months after admission, and 30 months after the onset of her illness. At one year follow up she remains well.

CASE 4

A girl, aged 9, was transferred from a paediatric

[redacted]

their *refusal* to walk, talk, eat, drink, or take care of themselves. The word refusal has been used advisedly. In no case was there any neurological deficit to account for the symptoms. Neither was there any suggestion of a postviral state. These children demonstrated a wilful, angry, or frightened component to their non-functioning. What then is the diagnosis and why were these children so ill?

Much further work is required to develop a really satisfactory system of classification for child psychiatric disorders.[1] In many instances it is difficult to fit a particular child's clinical picture into a specific diagnostic category. Such a lack of fit applies particularly in cases as complex and severe as these. Each child had certain features of a variety of different diagnoses, including anorexia nervosa, elective mutism, anxiety or phobic state, depression, conversion disorder, stupor, and post-traumatic stress disorder. However, none of these children fulfilled the diagnostic criteria for any of these conditions as defined in the *International Classification of Disease, 9th revision*[2] or the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition*.[3]

Anorexia nervosa and elective mutism are insufficient diagnoses in that each refers to a specific area of functioning (eating or talking) and these children had far more pervasive problems. Anxiety, phobic responses, and depression were undoubtedly features of the mental state of all these girls, although none of these terms alone seems adequate to describe their feeling state or their determinedly rejecting and self punitive behaviour. There were similarities with conversion disorder, which is characterised by alteration or loss of physical function that suggests physical disorder, but instead is apparently an expression of psychological conflict or need. Our children manifested a very obvious wilfulness in their symptoms, however, and in particular a pattern of refusal. Such determined and wilful refusal negates the diagnosis of conversion disorder, which is manifested by *inability* rather than volition.

Stupor is described by Lishman as a state of akinesis and mutism but with definite evidence of relative preservation of conscious awareness (p 8) and sometimes of a volitional nature.[4] In 'psychogenic stupor' signs of conversion hysteria are commonly in evidence, the condition may wax and wane, and there may be an appreciable emotional reaction when sensitive subjects are discussed. Completely passive dependence on others for feeding and toilet functions is rare, and the patient may show signs of irritation when moved against his will (p 198).[4] Although these children certainly fit these diagnostic criteria to some extent, we are not convinced that stupor is the correct diagnosis, if only because the criteria are so wide, and because the children showed such a wilful negativism.

A paper by Berrios on stupor may also be of help in understanding this condition.[5] He draws parallels between stuporose states and ethological models of freezing reactions, trance states, animal hypnosis, and tonic immobility, the latter being considered as a final step in the fear response against predation. Thus we might hypothesise that these children have adopted this posture as a final resort to escape an intolerable situation. This view is reinforced by the fact that we are currently treating two more children with a similar clinical picture, one of whom has finally been able to disclose that she has been sexually abused, but is clearly terrified of saying more. She has indicated that she and her mother would die if she told anyone exactly what had happened, and that she only feels safe in hospital having contact with no-one other than her mother and hospital staff.

The diagnostic criteria for post-traumatic stress disorder include the existence of a known stressor, re-experiencing of the trauma, numbing of responsiveness, or reduced involvement with the external world, and the presence of other symptoms such as hyperalertness, guilt, sleep disorder, cognitive difficulties, and avoidance behaviour. The obvious problem with making this diagnosis is the absence of any known definite stressor in all but one of the children. It would not be unreasonable to describe intrafamilial violence as a stressor, although by no means all children so exposed develop such serious illness.

Given that there is no completely satisfactory diagnosis it is clearly important to attempt to understand the aetiology. At presentation there were no obvious precipitating factors. Investigatin of the intrapsychic state of these children during the course of their admission revealed a fairly uniform picture.

Each child denied conflictual feelings, projected anger, and showed fear of attack. Their families were characterised by denial of any conflicts or other problems and yet had histories of intrafamilial violence.

The contribution of sexual abuse to these children's problems has to be considered. It was disclosed in one girl (case 2) and, given the physical signs, exceedingly likely in another (case 1). The history of alcohol abuse in the family of case 3, sexual threats in that of case 4, and intrafamilial violence in both, necessitates a high index of suspicion, but there is a major problem in obtaining corroborative information from mute, withdrawn and frightened children. The findings of Kiser *et al* seem to be of some relevance here.[6] They describe post-traumatic stress disorder when a reaction to sexual abuse as having three different forms of presentation:

(1) *Avoidance*: (a) restriction of affect, (b) withdrawal, (c) loss of interest, (d) aggression, (e) reluctance to talk, and (f) avoidance.

(2) *Re-experiencing*: (a) sex play, (b) talk and behaviour, (c) nightmares, (d) day dreams, and (e) flashbacks.

(3) *Autonomic hyperarousal*: (a) irritability, (b) aggression, (c) sleep problems, (d) anxiety, and (e) impaired concentration.

All the children fit into category 1, avoidance, with their pervasive refusal to participate in the normal activities of daily life, and each girl manifested some features of the other categories. It is also possible to conceptualise the refusal to eat and the resistance to washing and toileting as avoidance phenomena.

The aetiology of this condition is not completely clear but may involve a two stage process. The first is the trauma of sexual abuse, perhaps of a particularly sadistic nature, and the second is fear, induced by either a violent family member, threats, or the likely consequences of disclosure. The powerful silencing effects of threatened violence to a child cannot be underestimated. Summit vividly describes the plight of such children in his description of the child sexual abuse accommodation syndrome.[7] The syndrome is composed of five categories: (1) secrecy, (2) helplessness, (3) entrapment and accommodation, (4) delayed, unconvincing disclosure, and (5) retraction.

Three cases described by Brown and Perkins bear some similarity to ours in that all were girls who experienced a profound deterioration in their physical and mental state necessitating urgent hospitalisation and assessment for a degenerative disorder.[8] Their much younger ages, two being 5 and one 6·5 years old, allowed them to manifest uninhibited sexual play that led to rapid disclosure of sexual abuse in each case.

In older children the normal developmental decline in spontaneous play makes communication through that medium unlikely, and their cognitive development means that they can begin to weigh up the pros and cons of disclosure. At this age the children are caught between the developmental need to be within a family setting, while having the cognitive awareness that a disclosure is likely to break up their family. They are too old to disclose spontaneously, as did the children in the series of Brown and Perkin, and too young to be able to live independently of parents.

Discussions with colleagues have identified five more very similar cases to ours in girls aged between 11 and 15 (D Steinberg and D Black, personal communications) and we currently have two more such children on our ward. One of us (MT) has also recently seen a girl of 13 who had been mute and withdrawn for 10 years. After placement at a special boarding school she disclosed that she had been repeatedly and ritually sexually abused by several members of her extended family and threatened with death if she disclosed.

CONCLUSIONS

The multiplicity and severity of the symptoms in these children do not fit comfortably into any existing diagnostic category. The symptom complex can perhaps be understood as an extreme variation of so called avoidance behaviour seen in post-traumatic stress disorder. The inability to disclose even the existence, let alone the nature, of the trauma because of the threatened consequences may account for the extreme severity of the disorder. While awaiting further elucidation of how children react to and cope with such experiences, we suggest that it may be useful to recognise this discrete syndrome of pervasive refusal, as manifested by refusal to eat, drink, walk, talk, or participate in any activity including self care or toileting. It is most likely to occur in girls between the ages of about 9 and 14 years, in whom there is a possibility of sexual abuse, but who are terrified of disclosure because of threats of extreme violence.

Treatment must be in a hospital setting, where the child feels safe and can stay for as long as is necessary. Skilled psychiatric care and the availability of staff who are expert in exploring the possibility of sexual abuse are essential. There is no one specific form of treatment for children as ill as these. The mainstays of management include a combination of individual and family therapy, the use of the ward milieu, and medication as required. Whether or not such children can return home must depend on individual circumstances. The decision will be made on the basis of what is considered to be in the child's best interests. If the child expresses a clear wish to return home and there is no reason to believe that the child will be harmed at home, and the parents are able to accept and work on the fact that there is a psychological explanation for their child's illness, then a gradual return to the family home is indicated. If these circumstances do not apply serious consideration must be given to alternative placement. In any event such complex decisions are best made in the context of a series of case conferences held under child protection guidelines.

We thank the staff of the Mildred Creak Unit for their extremely skilled care of these children.

1 Rutter M, Gould M. Classification. In: Rutter M, Herson L, eds. *Child and adolescent psychiatry—modern approaches.* 1985. Oxford: Blackwell Scientific Publications, 1985:317.
2 Rutter M, Shaffer D, Shepherd M. A multiaxial classification of child psychiatric disorders. *International classification of diseases, 9th revision.* Geneva: WHO, 1975.
3 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 3rd Ed. Washington: American Psychiatric Association, 1980.
4 Lishman WA. *Organic psychiatry.* Oxford: Blackwell, 1978.
5 Berrios GE. Stupor revisited. *Compr Psychiatry* 1981;22: 466–78.
6 Kiser LA, Ackerman BJ, Brown E, *et al.* Post-traumatic stress disorder in young children: a reaction to purported sexual abuse. *American Academy of Child and Adolescent Psychiatry* 1988;27:645–9.
7 Summit R. The child sexual abuse accommodation syndrome. *Child Abuse Negl* 1983;7:177–93.
8 Brown R, Perkins M. Child sexual abuse presenting as organic disease. *BMJ* 1989;299:614–5.

Archives of Disease in Childhood 1991; **66:** 870–872

Intestinal permeability after single dose gluten challenge in coeliac disease

L Greco, G D'Adamo, A Truscelli, G Parrilli, M Mayer, G Budillon

Deparment of Paediatrics, University of Naples, Italy
L Greco
G D'Adamo
M Mayer

Sezione Autonoma di Epatologia, 2nd Medical Faculty of Naples, Italy
A Truscelli
G Parrilli
G Budillon

Correspondence to:
Dr L Greco,
Dipartimento di Pediatria,
Via S Pansini 5,
80131 Napoli,
Italy.

Accepted 12 December 1990

Abstract

The changes of intestinal permeability before and after a gluten load were studied. The study group comprised 27 patients with coeliac disease (mean age 12·3 years) and 19 healthy controls matched by sex and age. Intestinal permeability was studied by measuring the urinary excretion of two sugars, lactulose and L-rhamnose, before and six hours after the ingestion of five palatable biscuits made with 50 g of gluten powder. The patients with coeliac disease had been on a gluten free diet during the previous two years. After the gluten load lactulose and L-rhamnose urinary excretion changed significantly in patients, and a significant increase in the lactulose:L-rhamnose ratio was also observed. No significant changes were observed in the controls. In view of the modification of the three biopsies diagnostic protocol made by the European Society for Paediatric Gastroenterology and Nutrition, permeability tests associated with single gluten challenges may be an added contribution to the accuracy of the diagnosis in childhood.

Abnormalities of intestinal permeability have been shown by several authors in a series of gastroenterological diseases.[1–7] The sensitivity of the permeability test is considerable, as has been shown in transient gastrointestinal mucosa alterations such as those found in gastroenteritis.[8] Typical mucosal alterations of patients with coeliac disease are indeed responsible for considerable abnormalities in sugar permeability.[1 9 10]

Passive intestinal permeability can be studied in man by various probe markers: polyethyleneglycol 400, ^{51}Cr-EDTA, mannitol, cellobiose, lactulose, or L-rhamnose.[7–14] All are excreted nearly unmodified in urine. Lactulose (with a molecular weight of 340) permeates the intestinal mucosa through large 'pores' of low incidence, which are probably associated with the paracellular 'tight junction' complexes. Less than 1% of ingested lactulose permeates the intestinal mucosa and appears in the urine. L-Rhamnose is a monosaccharide (with a molecular weight of 164) which permeates mainly via a transcellular route through smaller water filled pores in the enterocyte cell walls that larger molecules, such as lactulose, cannot penetrate. Intestine mucosal damage decreases the area for absorption. This is a factor which negatively influences the high transcellular permeation of small molecules like L-rhamnose. It increases the incidence of large pores (paracellular and extrusion cell zones) which enhances the passive permeation of large molecules like lactulose.[14] The ratio of lactulose:L-rhamnose in urine is appreciably raised during severe derangement of intestinal integrity and allows an excellent diagnostic discrimination of patients with severe gut disease.

Sugar permeability has been extensively used in the adult gastroenterological patient, but fewer reports are available about its application in the paediatric patient.[15] Hamilton *et al* studied children with coeliac disease and cows' milk intolerance and showed the low specificity of the test.[16] Adult coeliac patients have been studied by the same group in different phases of the disease. Sugar permeability improves with the start of the gluten free diet and deteriorates with the reintroduction of gluten in the diet. Six adult patients were challenged with a single dose of gluten and their permeability was assessed before and 24 hours after the challenge. All showed a significant gluten induced modification. The authors concluded that a single dose gluten challenge with an intestinal permeability evaluation could be an adequate substitute for the recommended long term challenge.[16] Gluten challenge has been proved to be associated with a consistent reduction of growth velocity in children, with clinically relevant symptoms, and with a considerable degree of anxiety in children and families.[17]

The objective of this study was to evaluate the intestinal permeability by an oral load of lactulose and L-rhamnose in patients with coeliac disease after a single dose of gluten. The aim was to minimise the time and damage caused by prolonged gluten challenge in these subjects.

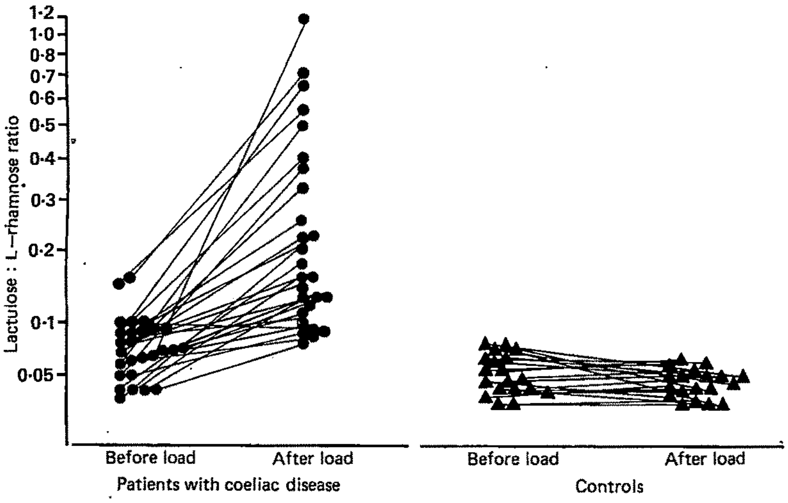
Subjects and methods

Twenty seven patients with coeliac disease participated in the study. They were included in the study if (1) they were aged 7 years or above and were aware of what a gluten challenge would involve. (2) The diagnosis of coeliac disease had been confirmed by a full diagnostic protocol with flat mucosal biopsy in the florid phase and histological relapse on gluten challenge, according to the indications of the European Society for Paediatric Gastroenterology and Nutrition (1982). (3) They had been on a gluten free diet for at least two years. (4) Antigluten antibodies were within normal limits. Nineteen healthy subjects were recruited as controls and they were age and sex matched with the cases.

Excretion vaues before and after gluten challenge. Results are mean % oral dose (95% confidence intervals)

	Lactulose	*L-rhamnose*	*Lactulose:L-rhamnose ratio*
Controls:			
Before gluten	0·29 (0·32 to 0·25)	5·63 (6·14 to 5·11)	0·052 (0·06 to 0·04)
After gluten	0·27 (0·30 to 0·24)*	5·93 (6·44 to 5·42)*	0·045 (0·05 to 0·04)*
Mean change†			−9·3 (−11·8 to −6·8)
Patients with coeliac disease:			
Before gluten	0·43 (0·48 to 0·37)	4·94 (5·62 to 4·26)	0·106 (0·15 to 0·07)
After gluten	0·65 (0·79 to 0·52)**	2·87 (3·43 to 2·03)***	0·316 (0·42 to 0·21)***
Mean change†			+240 (260 to 220)

Student's *t* test for paired samples before and after gluten (log transformed values).
*$p>0·2$, **$p<0·005$, ***$p<0·00001$.
†Mean change has been calculated as the antilog of the log transformed value of the percent ratio change before and after the gluten load.



Lactulose:L-rhamnose ratio before and after gluten load in patients with coeliac disease and in controls.

PROCEDURE

Intestinal permeability was assessed twice: once after an overnight fast before the gluten challenge and again six hours after the ingestion of five palatable biscuits made with 50 g of gluten powder that was wheat germ free (Salsa), cooked with sugar and flavours but no yeast. The bladder was emptied, and 5 g of lactulose and 1 g of L-rhamnose dissolved in 100 ml water were administered. The solution was nearly isotonic (220 mosm/l). The osmolarity of the test solution was kept below the level known to induce an alteration of intestinal permeability or motility.[5] A five hour urine collection was performed, the volume was recorded, and a sample, preserved with thiomersal (Merthiolate, 1 mg/10 ml urine), was stored at −20°C before analysis using a method previously described.[5] The conditions used were a starting temperature of the oven at 110°C, with an increase of 3°C/minute up to 255°C, injector temperature 275°C, detector temperature 305°C, gas carrier (nitrogen) flow 35 ml/min, attenuation input 1:100 and output 1:2, and back off 1:100.

The lactulose retention time relative to that of turanose was 0·92, and the retention time of L-rhamnose relative to that of 3-O-methyl-D-glucose was 0·79.

STATISTICAL ANALYSIS

All study variables were assessed for normality. The distribution of lactulose, L-rhamnose, and the ratio before the challenge did not show any major skewness. The values after the challenge, in cases but not in controls, showed a significant skewness when compared with a normal distribution. A log transformation was therefore adopted in order to reduce the skewness for the data of all the groups when differences between the means were assessed.

Results

No sex difference was noted in the two groups. Mean age was 13·8 (range 5–24) in controls and 12·3 (range 7–21) in cases. The frequency distribution of age in cases was not significantly different than the controls (χ^2 test). None of the controls showed any discomfort after gluten ingestion. Ten cases did show significant disturbances, mostly transient vomiting and abdominal pain two hours after gluten ingestion.

Before gluten challenge, permeability was normal in all controls and in 25/27 cases. The two cases with abnormal permeability before the challenge (lactulose:L-rhamnose ratio above 0·1) claimed to be on a strict gluten free diet. The L-rhamnose excretion before the challenge was not statistically different in cases compared with controls (unpaired Student's *t* test), while the lactulose excretion showed a statistical difference between the two groups (unpaired *t* test=−3·9, $p<0·001$). After the gluten challenge, the controls showed on average no alteration of their permeability (no statistical difference for lactulose, L-rhamnose, and the ratio). In the patients with coeliac disease the lactulose excretion increased about 50%, the L-rhamnose halved, and the ratio almost trebled (table).

If the limit of the mean+1·96 SD of the lactulose:L-rhamnose ratio of the controls after the challenge (0·0646) is assumed as the level of normal absorption, none of the cases show a normal absorption after gluten challenge. All the controls are within normal limits after having ingested the same amount of gluten biscuits. The figure shows the distribution of the lactulose:L-rhamnose ratio in cases and controls before and after the gluten challenge.

Discussion

A hypertonic test solution was often adopted to increase sensitivity in adults,[18 19] while experience in most investigations of children is actually confined to the use of an isotonic test solution to avoid the modifications that the hyperosmolarity would induce in vivo.[10] Recently Hodges *et al* demonstrated that a hypertonic sugar absorption test is well tolerated even by young children.[20]

Intestinal permeability was outside the normal range in all treated subjects with coeliac disease after the challenge. Two of them showed significantly higher values than controls before gluten challenge. They claimed to be on a gluten free diet. Minor permeability alterations have often been described in treated coeliac patients.[9 16]

The single dose load of a consistent amount of gluten powder that was free of wheat germ does not produce any permeability change in healthy controls. It produces a consistent alteration of the intestinal permeability in most of the cases, including the ones with slightly abnormal permeability before the challenge.

The lactulose:L-rhamnose ratio allows a good discrimination between cases and controls after the gluten challenge. Cases who developed temporary symptoms on gluten ingestion did not show a higher ratio after the challenge than the whole coeliac group. In five of these cases, the ratio after challenge ranged from 0·09 to 0·20, in three there was a very clear rise in the ratio due to the challenge (from 0·095 to 0·14, from 0·07 to 0·095, and from 0·09 to 0·21) and in two cases the ratio moved from 0·09 to 0·11. A biological variation of the response to gluten ingestion is not uncommon in studies of coeliac disease.

Results from 27 cases are not enough to state anything about specificity and sensitivity, but the observed differences are sufficiently consistent to make the test a useful tool to evaluate gluten challenge in coeliac children. Those subjects responding sufficiently strongly to the test can be regarded as successful and the few others, who respond less sharply, should go on to a formal long term gluten challenge.

Sensitivity to gluten in patients with coeliac disease is often age dependent and children appear to be more sensitive than adults to occasional gluten introduction. For this reason a single dose of gluten is likely to produce an intestinal response in coeliac children. Histological abnormalities may not have sufficient time to develop after a single dose of gluten, but physiological mechanisms may well be affected by the offending agent.

The response to gluten, in most of our cases, was not moderate or borderline, but sharp and consistent.

The final confirmation of the diagnosis of coeliac disease in children is much too important for the child to be based on the results of a single test, with no mucosal evaluation, as suggested by Hamilton *et al.*[16] We found, from a cohort of 426 cases, that after a mucosal relapse further challenges were required by teenage coeliacs and their families in order to maintain the diet. Many of these tests may be carried out in the future with no invasive techniques by a single dose gluten challenge and permeability evaluation. We have previously used the combination of antigluten antibodies with oral xylose load to follow up the gluten challenge,[21] but most cases required at least two months to show a clear relapse. Although no symptoms appeared in such a time interval, growth arrest occurred in a few patients. A six hour gluten challenge does reduce the effect on the patient and make the challenge a routine ambulatory test with an answer within a few days. More work will help to identify the best gluten dose and osmolality of the sugar solution to improve the sensitivity of the test, but no absolutely perfect method will remove the biological variability in the expression of the intestinal permeability.

1 Menzies IS, Laker MF, Pounder R, *et al.* Abnormal intestinal permeability to sugars in villous atrophy. *Lancet* 1979;**ii:** 1107–9.
2 Cobden J, Rothwell J, Axon ATR. Intestinal permeability and screening tests for coeliac disease. *Gut* 1980;**21:**512–8.
3 Jackson PG, Lessof MH, Baker RWR, Ferret J, MacDonald DM. Intestinal permeability in patients with eczema and food allergy. *Lancet* 1983;**i:**1285–6.
4 Ukabam SO, Clamp JR, Cooper BT. Abnormal small intestinal permeability to sugars in patients with Crohn's disease of the ileum and colon. *Clin Sci* 1982;**61:**21–2P.
5 Parrilli G, Cuomo R, Nardone G, Maio G, Izzo CM, Budillon G. Investigation of intestine function during acute viral hepatitis using combined sugar oral loads. *Gut* 1987;**28:** 1439–44.
6 Budillon G, Parrilli G, Pacella M, Cuomo R, Menzies IS. Investigation of intestine and liver function in cirrhosis using combined sugar oral loads. *J Hepatol* 1985;**1:**513–24.
7 Chadwick VS, Phillips SF, Hofmann AF. Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). II. Application to normal and abnormal permeability states in man and animals. *Gastroenterology* 1977;**73:**247–51.
8 Cobden J, Dickinson RJ, Rothwell J, Axon ATR. Intestinal permeability assessed by excretion ratios of two molecules: results in coeliac disease. *BMJ* 1978;**ii:**1060.
9 Bjarnason I, Marsh MN, Price A, Levi AJ, Peters TJ. Intestinal permeability in patients with coeliac disease and dermatitis herpetiformis. *Gut* 1985;**26:**1214–9.
10 Bjarnason I, Peters TJ. In vitro determination of small intestinal permeability: demonstration of a persistent defect in patients with coeliac disease. *Gut* 1984;**25:**145–50.
11 Hamilton I, Hill A, Bose B, Bouchier AD, Forsyth JS. Small intestinal permeability in pediatric clinical practice. *J Pediatr Gastroenterol Nutr* 1987;**6:**697–701.
12 Strobel S, Brydon WJ, Ferguson A. Cellobiose/mannitol sugar permeability test complements biopsy histopathology in clinical investigation of the jejunum. *Gut* 1984;**25:** 1241–6.
13 Ford RPK, Menzies IS, Phillips AD, Walker-Smith JA, Turner MW. Intestinal sugar permeability: relationship to diarrhoeal disease and small bowel morphology. *J Pediatr Gastroenterol Nutr* 1985;**4:**568–74.
14 Maxton DG, Bjarnason I, Reynolds AP, Catt SD, Peters DJ, Menzies IS. Lactulose, 51Cr-labelled ethylenediaminetetra acetate, L-rhamnose and polyethyleneglycol 500 as probe markers for assessment in vivo of human intestinal permeability. *Clin Sci* 1986;**71:**71–80.
15 Nathavitharan KA, Lloyd DR, Raafat F, Brown GA, McNeish AS. Urinary manitol:lactulose excretion ratios and jejunal mucosal structure. *Arch Dis Child* 1988;**63:** 1054–7.
16 Hamilton I, Cobden I, Rothwell J, Axon ATR. Intestinal permeability in coeliac disease: the response to gluten withdrawal and single-dose gluten challenge. *Gut* 1982;**23:** 202–10.
17 Greco L, Mayer M. Linear and catch up growth in chronically ill children. In: Susanne C, ed. *Genetic and environmental factors during the growth period.* Brussels: Plenum Press, 1984:133–43.
18 Cobden I, Hamilton I, Rothwell J, Axon ATR. The cellobiose/mannitol test: physiological properties of probe molecules and influence of extraneous factors. *Clin Chim Acta* 1985;**148:**53–62.
19 Laker MF, Menzies IS. Increase in human intestinal permeability following ingestion of hypertonic solutions. *J Physiol (Lond)* 1977;**265:**881–94.
20 Hodges S, Ashmore SP, Patel HR, Tanner MS. Cellobiose: mannitol differential permeability in small bowel disease. *Arch Dis Child* 1989;**64:**853–5.
21 Mayer M, Greco L, Troncone R, Grimaldi M, Pansa G. Early prediction of relapse during gluten challenge in childhood coeliac disease. *J Pediatr Gastroenterol Nutr* 1989;**8:**474–9.

MONATSSCHRIFT KINDERHEILKUNDE

139. Band Heft 4
April 1991

Organ der
Deutschen Gesellschaft
für Kinderheilkunde

Thema des Monats

Infektionskrankheiten — diagnostische Verfahren

S. Wirth, K. M. Keller, W. Baumann, B. Zabel
Hepatitis-B-Virus-DNS. Aktuelle Diagnostik bei Kindern mit chronischer Hepatitis B 202

A. Kaufhold, E. Krug, R. Lütticken, U. Knoop, F. Bläker
Bewertung von Schnelltests zum Direktnachweis des Gruppe-A-Streptokokkenantigens in Rachenabstrichen. Untersuchung zu vier kommerziellen Testsystemen 208

Pädiatrie aktuell

Vergleich zwischen Kernspintomographie und endokrinen Störungen bei Erkrankungen des Hypothalamus-Hypophysen-Systems
Was ist die richtige Lagerung des Säuglings beim gastroösophagealen Reflux?
Für und Wider eines Neugeborenen-Screenings auf zystische Fibrose 214

Was hat das Kind?

Trainingsprogramm für die Weiterbildung zum Kinderarzt 215

Klinik und Forschung

K. Berger, D. Harms, H. Denk, J. D. Beck
Impulszytophotometrische Bestimmung des DNA-Gehaltes von paraffinfixierten Neuroblastomen 216

W. Andler
Autonome Ovarialzysten und Pseudopubertas praecox 220

K. E. v. Mühlendahl
Die Feersche Krankheit 224

Der interessante Fall

Th. Paul, A. Reimer, M. Wilken, K. Miller, H. C. Kallfelz
Komplexer zyanotischer Herzfehler bei einem Neugeborenen mit einem Cat-Eye-Syndrom 228

A. Siermann, W. Storm
Toxisches Schocksyndrom bei einem 6jährigen Jungen 231

G. Kurlemann, G. Bongartz, W. Krings, D. G. Palm
Das asymptomatische Moyamoya-Syndrom 235

H. Skopnik, P. Greven, L. Füzesi, R. Mertens, G. Heimann
Gastrointestinale Symptome bei disseminierten Langerhans-Zell-Histiozytosen. Kasuistik und Literaturübersicht 239

Wußten Sie schon?

Aus der Klinik — für die Klinik

L. Schuchmann, W. Pernice, Ch. Hufschmidt, C. P. Adler
Arthritis tuberculosa — eine seltene, aber wichtige Differentialdiagnose zur juvenilen chronischen Arthritis (JCA) 244

Was hat das Kind?

Auflösung und Kommentar des Trainingsprogramms 251

Briefe an die Redaktion — Diskussionen 248
Aus Gesellschaften und Berufsverband 251
Tagesgeschichte, Personalia 253
Tagungskalender 253

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Hong Kong Barcelona Budapest

Annual subscription: DM 298,- plus postage

European Journal of
Pediatrics
Incorporating
Acta Paediatrica Belgica
and
Helvetica Paediatrica Acta

Volume 150 No. 6 1991

The pioneers of pediatric medicine
379

Review

The treatment of minimal change nephrotic syndrome: lessons learned from multicentre cooperative studies
J. Brodehl 380

Cardiology

Myocardial β-adrenoceptor density and the distribution of β_1- and β_2-adrenoceptor subpopulations in children with congenital heart disease
R. Kozlik, H. H. Kramer, H. Wicht, A. Krian, J. Ostermeyer, D. Reinhardt
388

Endocrinology

Determination of thyroid volume by ultrasound from the neonatal period to late adolescence
J. P. Chanoine, V. Toppet, R. Lagasse, M. Spehl, F. Delange 395

Isolated adrenocorticotropic hormone deficiency associated with common variable immunodeficiency
P. A. Tovo, R. Lala, S. Martino, G. Pastorelli, C. De Sanctis 400

Oral glucose tolerance testing in cystic fibrosis: correlations with clinical parameters and glycosylated haemoglobin determinations
J. De Schepper, I. Dab, M. P. Derde, H. Loeb 403

Gastroenterology/Hepatology

What will be the adult height of coeliac patients?
E. Cacciari, G. R. Corazza, S. Salardi, M. G. Pascucci, M. Tacconi, A. Cicognani, D. Tassinari, G. Biasco, U. Volta, R. Lazzari, G. Gasbarrini
407

Dumping syndrome after combined pyloroplasty and fundoplication
K. Pittschieler 410

Hematology/Oncology

Percentile curves for red cell indices of β°-thalassaemia heterozygotes in infancy and childhood
R. Galanello, F. Lilliu, F. Bertolino, A. Cao 413

Detection of multidrug-resistant protein, P-glycoprotein in childhood leukaemia and lymphoma
Y. Mizuno, T. Hara, M. Nagata, A. Tawa, T. Tsuruo, K. Ueda
416

Immunology/Allergology

Griscelli disease with cerebral involvement
Á. Haraldsson, C. M. R. Weemaes, J. A. J. M. Bakkeren, R. Happle
419

Bacille Calmette-Guérin – associated neonatal hepatitis
B. Simma, O. Dietze, W. Vogel, H. Ellemunter, J. P. Guggenbichler
423

Metabolic diseases

Inadequate iron availability as a possible cause of low serum carnitine concentrations in patients with phenylketonuria
H. Böhles, K. Ullrich, W. Endres, A. W. Behbehani, U. Wendel
425

A case of abetalipoproteinaemia in a Polish family
M. Kaciński, F. Kaczmarski, W. Mieżyński, Z. Grzenda-Adamek, B. Miszczuk-Jamska, J. Stopyrowa, J. Sznajd 429

Neonatology

Factors influencing the clinical response to surfactant replacement therapy in babies with severe respiratory distress syndrome
Collaborative European Multicentre Study Group 433

Inflation time in mechanical ventilation of preterm neonates
M. Hird, A. Greenough 440

Nephrology

Renal growth and function 11–28 years after treatment of Wilms' tumour
A. Mäkipernaa, O. Koskimies, J. Jääskeläinen, A.-M. Teppo, M. A. Siimes 444

Pneumology

Unexpected side-effects of inhaled steroids: a case report
K. Priftis, M. L. Everard, A. D. Milner
448

Letters to the editors

Delayed splenic development or transient asplenia?
S. Özsoylu 450

Reply
M. Fevzi Ozkaynak, A. Ortega 450

Indexed in *Current Contents*

Springer International

Subscription information

Volume 150 (12 issues) will appear in 1991. Information about obtaining back volumes and microform editions available upon request.

North America. Annual subscription rate: approx. US $ 1060.00 (single issue price approx. $ 102.00), including carriage charges. Subscriptions are entered with prepayment only.

Orders should be addressed to:
Springer-Verlag New York Inc.
Service Center Secaucus
44 Hartz Way
Secaucus, NJ 07094, USA
Tel: (201) 348-4033
Telex 023125994
FAX (201) 348-4505

All other countries. Annual subscription rate: DM 1598.00 plus carriage charges; Federal Republic of Germany: DM 27.61 incl. value added tax; all other countries: DM 60.60 except for the following countries to which SAL delivery (Surface Airmail Lifted) is mandatory: Japan DM 125.40, India DM 96.60, Australia/New Zealand DM 141.00. Airmail delivery to all other countries is available upon request. Volume price: DM 1598.00, single issue price: DM 159.80 plus carriage charges. Subscriptions can either be placed via a bookdealer or sent directly to:

Springer-Verlag
Heidelberger Platz 3, 1000 Berlin 33, FRG
Tel. (0)30/8207-0, Telex 183319
FAX (0)30/8214091

Archives of Disease in Childhood 1991; **66:** 873–875

Alteration of urinary carnitine profile induced by benzoate administration

Toru Sakuma

Abstract

To study the effect of sodium benzoate on carnitine metabolism, the acylcarnitine profile in the urine of five normal volunteers and two patients with urea cycle disorders was examined with fast atom bombardment-mass spectrometry. The volunteer subjects were given 5 g of sodium benzoate orally and the two patients with urea cycle disorders (carbamyl phosphate synthetase deficiency type I and ornithine transcarbamylase deficiency) were already undergoing treatment with sodium benzoate and L-carnitine. The amount of benzoylcarnitine excretion depended on the dose of both sodium benzoate and L-carnitine in a reciprocal relation. Increased excretions of

Case reports

Case 1 was a 4 year old Japanese boy of unrelated parents. At the age of 3 days he was transported to our hospital because of coma with pulmonary haemorrhage. On admission his blood ammonia concentration was appreciably raised (503 μmol/l) but his urinary orotate was not increased. For the analysis of urea cycle enzyme activities[7] a liver biopsy was performed at the age of 3 months, which confirmed a diagnosis of carbamyl phosphate synthetase deficiency type I (0·1% of control activity). His blood ammonia concentration was maintained at <30 μmol/l by a restricted protein diet, arginine, and sodium benzoate until the time of the study when the patient was aged 4 years.

[redacted]

ammonia to 87 µmol/l. The dose of sodium benzoate was then increased to 300 mg/kg/day; this led to a fall in blood ammonia to within the normal range. Throughout the period of study the child remained asymptomatic and was maintained on intravenous L-carnitine at the dose of 25 mg/kg/day.

Case 2 was a 2 year old Japanese boy of unrelated parents. He presented at the age of 2 days with lethargy and convulsions. His blood ammonia concentration was 334 µmol/l and urinary orotate was remarkably increased (91·5–354·0 µg/mg creatinine). The concentration of plasma citrulline was decreased. The diagnosis of ornithine transcarbamylase deficiency was established on the basis of enzyme assay of a liver biopsy specimen (activity 1% of control). He was treated with a low protein diet and sodium benzoate (200 mg/kg/day). He remained asymptomatic and has shown normal growth. When he was 2 years old, hypocarnitinaemia of 1·0–3·0 µmol/l was noticed and an L-carnitine supplement of 50 mg/kg/day was started.

Five male volunteers who were on no medication and in good health were enrolled in the study to assess the short term effect of sodium benzoate administration. Informed consent was obtained from all of them. Their mean (SD) age was 23 (2) years and they weighed 65 (5) kg. Sodium benzoate (5 g) was orally administered after overnight fasting. Blood and urine samples were taken at various intervals (0, 2, 4, 6, and 24 hours after the load).

Methods

All serum and urine samples were stored at −20°C for subsequent analysis. Blood ammonia concentration was measured by the glutamate dehydrogenase method. Urinary hippurate was assayed by the colorimetric method.[8] All the reagents used were of reagent grade.

URINARY ACYLCARNITINE PROFILE

D3-carnitine ($^2H_3$-Me_1-N:carnitine) was the kind gift of the Earth Chemical Company, Hyogo, Japan. Acetyl-D3-carnitine and propionyl-D3-carnitine were synthesised with each acylchloride and D3-carnitine by a similar method to the benzoyl-D3-carnitine synthesis described previously.[6] These authentic acyl-D3-carnitines were over 95% in purity when assayed by the carboxylic acid analyser with an ODS column.[9] Urinary concentrations of carnitine derivatives, whose methyl esterification were done by deuterium exchanged methanol (CD30D), were quantified with fast atom bombardment-mass spectrometry (JMS-DX 300; JMA-DA 3500, JEOL, Tokyo, Japan) by the stable isotope dilution techniques as described by Montgomery and Mamer.[10] By this analytical procedure, because the one fragment ion signal of both labelled and unlabelled benzoylcarnitine-D3-methyl ester (M-62, M-59, respectively) is just the same as that of acetyl-D3-carnitine-D3-methyl ester (m/z=224), these two compounds are indistinguishable. Additionally, the maximal strength of each acylcarnitine signal has a different scanning time. To make a quantitative analysis of acylcarnitine, each acyl-D3-carnitine should be used as its own internal standard. For a quantification of acetyl, propionyl, and benzoylcarnitine, therefore, acetyl-D3-, propionyl-D3-, or benzoyl-D3-carnitine was used as an internal standard in each sample. By this procedure the calibration curve of acetyl, propionyl, and benzoylcarnitine was linear over the sample concentration range from 1 to 500 nmol/ml.

STATISTICAL ANALYSIS

Each value represented the mean (SE). Values of the two groups were compared with the Student's *t* test. Unless indicated otherwise the level of significance was set at $p<0·05$.

Results

In case 1 a slightly reduced urinary excretion of hippurate was noted after lowering the dose of sodium benzoate (50 mg/kg/day). This rapidly increased again when the dose was augmented to 300 mg/kg/day. The excretion pattern of benzoylcarnitine was almost the same as that of hippurate (fig 1). Acetylcarnitine and propionylcarnitine concentrations in urine also changed similarly to benzoylcarnitine, but their amounts were reduced gradually even though the same dose of sodium benzoate was given.

In case 2, as shown in fig 2, a large amount of propionylcarnitine and acetylcarnitine but only a small amount of benzoylcarnitine (43 µmol/g creatinine) was excreted in urine when sodium benzoate was given without L-carnitine administration. Benzoylcarnitine excretion increased to 10-fold by the addition of L-carnitine and the hippurate excretion also increased to a lesser degree.

In the volunteers the excretion of acetylcarnitine and propionylcarnitine increased rapidly and reached the maximum point at two hours after loading (that is, 7·5-fold and 22-fold, respectively). The excretion of both hippurate and benzoylcarnitine were slightly slow and reached the maximum at four hours after loading (table).

Carnitine derivatives and hippurate in urine after sodium benzoate loading test in volunteers. Results are mean (SE)

	Time after load (hours)				
	0	*2*	*4*	*6*	*24*
Acetylcarnitine (nmol/mg creatinine)	13·1 (4·2)	97·8 (23·2)*	94·7 (26·4)*	28·4 (10·2)	28·5 (4·9)
Propionylcarnitine (nmol/mg creatinine)	9·0 (2·4)	200·0 (41·5)*	179·3 (52·4)*	20·9 (3·7)	11·8 (4·3)
Benzoylcarnitine (nmol/mg creatinine)	1·9 (0·4)	34·2 (13·2)*	67·4 (21·5)*	51·8 (18·2)	3·1 (0·7)
Hippurate (µmol/mg creatinine)	3·9 (0·6)	205·0 (41·7)*	221·1 (47·8)*	32·2 (7·2)*	2·2 (0·4)

*Significant difference from baseline.

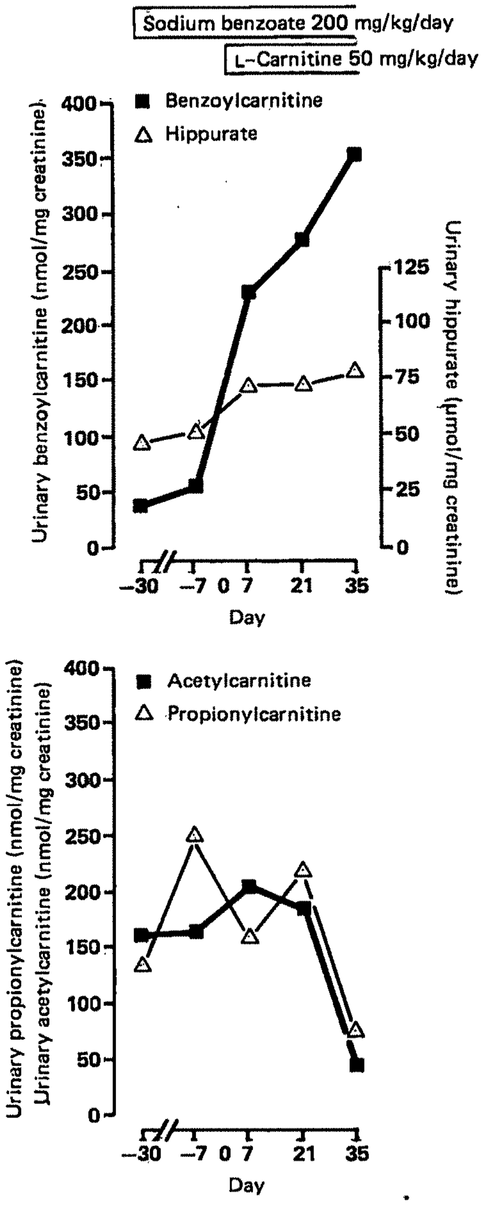


Figure 2 Case 2: treated with oral sodium benzoate at the dose of 200 mg/kg/day, L-carnitine was started from day 0 at 50 mg/kg/day. Upper graph: benzoylcarnitine excretion was increased about 10 times by the carnitine supplementation and more hippurate was also excreted than at 0 hours. Lower graph: both concentrations were very high but were replenished after L-carnitine supplement.

Discussion

Because benzoyl-CoA conjugates with glycine to be excreted as hippurate into the urine, sodium benzoate has been used for the treatment of hyperammonaemia.[1,2] Recently we reported that a certain amount of benzoylcarnitine was excreted in the urine of a patient with carbamyl phosphate synthetase deficiency type I on benzoate treatment.

In this investigation a relatively large amount of benzoylcarnitine could be detected in urine of volunteers receiving sodium benzoate as well as from two patients with urea cycle disorders. Therefore, benzoylcarnitine might be another important product (0·5 to 7%) of benzoate and its excretion in urine is a possible cause of hypocarnitinaemia associated with long term benzoate treatment for hyperammonaemic patients. In addition, increased acetylcarnitine and propionylcarnitine excretions were also recognised both in patients and volunteers. The sum of these three carnitine derivatives accounted for the majority of increased esterified carnitines. Thus the increase in excretion of acetylcarnitine and propionylcarnitine, plus benzoylcarnitine excretion, might be another cause of hypocarnitinaemia in benzoate treatment.

These phenomena could be explained as follows. Acyl-CoAs were catalysed with carnitine then formed corresponding acylcarnitines according to the equation below:

$$[\text{acyl-CoA}][\text{carnitine}]=k\,[\text{acylcarnitine}][\text{CoA-SH}]$$

where k is a constant. As amounts of acylcarnitine were excreted into the urine after benzoate administration in volunteers and in patients, both the increased influx of carnitine into mitochondria and the decrease of the acyl-CoA concentration were predicted, which is consistent with the data of in vitro study on rats.[11,12]

An unexpected observation was the finding of large amounts of propionylcarnitine in urine rather than acetylcarnitine. Although this important change was induced by the administration of sodium benzoate, the cause of it was obscure.

Sodium benzoate has been administered to hyperammonaemic patients. It is also important not to overlook the adverse potential for mitochondrial functions and to administer it appropriately. In the present study it was confirmed that the alteration of carnitine metabolism could generally be induced by benzoate administration and that its analysis might be useful to examine the effect of benzoate on mitochondria in vivo. These results suggested that L-carnitine supplementation should be considered to correct a carnitine shortage as well as to preserve an adequate intramitochondrial CoA profile.

Thanks go to Dr Naruji Sugiyama, Dr Takashi Ichiki, Dr Masanori Kobayashi, and Dr Yoshiro Wada for discussion of the manuscript. Thanks are also due to Dr Yoshimi Suzuki and Dr Yutaka Nishimura (department of paediatrics, Toyohashi City Hospital) for providing specimens from case 2.

1 Brusilow SW, Valle DL, Batshaw ML. New pathway of nitrogen excretion in inborn errors of urea synthesis. *Lancet* 1979;ii:452–4.
2 Brusilow SW, Tinker J, Batshaw ML. Amino acid acylation: a mechanism of nitrogen excretion in inborn errors of urea synthesis. *Science* 1980;207:659–61.
3 Mazuda I, Ohtani Y, Ohyanagi K, *et al.* Hyperammonemia related to carnitine metabolism with particular emphasis on ornithine transcarbamylase. *Enzyme* 1987;38:251–5.
4 O'Connor JE, Costell M, Glisolia S. The potentiation of ammonia toxicity by sodium benzoate is prevented by L-carnitine. *Biochem Biophys Res Commun* 1987;145:817–24.
5 Cyr DM, Maswoswe SM, Tremblay GC. Inhibition of the urea cycle and de novo pyrimidine biosynthesis by sodium benzoate. *J Inherited Metab Dis* 1987;10:308–10.
6 Sakuma T, Asai H, Ichiki T, *et al.* Identification of benzoylcarnitine in the urine of a patient of hyperammonaemia. *Tohoku J Exp Med* 1989;159:147–51.
7 Cohen NS, Cheung CW, Raijman L. The effects of ornithine on mitochondrial carbamyl phosphate synthesis. *J Biol Chem* 1980;255:10248–55.
8 Tomokuni K, Ogata M. Direct colorimetric determination of hippuric acid in urine. *Clin Chem* 1972;18:349–52.
9 Kidouchi K, Sugiyama N, Morishita H, *et al.* Identification of glutarylcarnitine in glutaric aciduria type 1 by carboxylic acid analyzer with an ODS reverse-phase column. *Clin Chim Acta* 1987;164:261–6.
10 Montgomery JA, and Mamer OA. Measurement of urinary free and acylcarnitine: quantitative acylcarnitine profiling in normal humans and in several patients with metabolic errors. *Anal Biochem* 1989;176:85–95.
11 McCune SA, Drunt PJ, Flanders LE, *et al.* Inhibition of hepatic gluconeogenesis and lipogenesis by benzoic acid, p-tetr-butylbenzoic acid, and a structurally related hypolipidemic agent SC-33459. *Arch Biochem Biophys* 1982;214: 124–33.
12 Swartzentruber MS, Harris RH. Inhibition of metabolic processes by coenzyme-A-sequestering aromatic acids. *Biochem Pharmacol* 1987;36:3147–53.

Archives of Disease in Childhood 1991; **66:** 876–878

Clinical predictors and radiological reliability in atlantoaxial subluxation in Down's syndrome

K A Selby, R W Newton, S Gupta, L Hunt

Abstract

Clinical signs and symptoms that might predict atlantoaxial subluxation were studied prospectively in 135 of 180 children with Down's syndrome aged 6–14 years who form the Hester Adrian Research Centre cohort. Lateral radiographs of the cervical spine were taken in flexed, extended, and neutral positions, and the percentage of abnormalities in each view was 14, 10, and 10%, respectively. Gait was the only significant clinical predictor. The relative risk of having an abnormal neck radiograph with an abnormal gait was 2·91 (95% confidence interval (CI) 1 to 8). The sensitivity was 50% and the specificity 81%. Nineteen children had repeat radiographs to assess the reliability of radiological diagnosis. Six had abnormalities; five of 19 (26%) had an abnormality on the first radiograph, and four of 19 (21%) had an abnormality on a second radiograph, but only three (15%) had an abnormality on both occasions in any view (95% CI 0 to 25).

We conclude that radiographs of the cervical spine are unreliable at identifying atlantoaxial subluxation in children with Down's syndrome, and we failed to identify any reliable clinical predictor.

Atlantoaxial subluxation has been reported to occur in 9·5–27% of individuals with Down's syndrome,[1-4] [6] although symptomatic dislocation has rarely been reported. The association of atlantoaxial subluxation with Down's syndrome was noted in the 1960s when Spitzer *et al* described forward displacement of the atlas on the axis.[7] Atlantoaxial subluxation may be a manifestation of hypotonia and joint laxity that occurs in children with Down's syndrome allowing increased mobility between the atlas and the axis during flexion and extension of the neck. Abnormalities of the odontoid process of the axis may also play a part.[8] When atlantoaxial subluxation occurs it may also cause compression of the spinal cord. The incidence has been reported as 1·5% in an unselected study on 404 individuals with Down's syndrome.[6]

Previous studies have reported on hospital based populations, and the incidence of abnormality may therefore be artificially high. A recent community based study of adults sought a correlation between radiological and neurological abnormality.[9] The neurological testing was, however, less detailed and less sensitive than in the present study. Furthermore, to reflect the underlying improvement of atlantoaxial subluxation with age a stricter definition was used (atlantodens distance >3 mm).

Royal Manchester and Booth Hall Children's Hospitals, Manchester
K A Selby
R W Newton
S Gupta
L Hunt

Correspondence to:
Dr K A Selby,
Department of Paediatric Neurology,
Queen's Medical Centre,
Nottingham NG7 2UH.

Accepted 1 February 1991

We chose to study a population based group that had already been validated as a cohort. We hoped to identify simple clinical parameters that could be used by senior clinical medical officers to identify the problem within the community. No previous studies to our knowledge have prospectively sought predictive signs.

In 1984 the Committee on Sports Medicine of the American Academy of Pediatrics published recommendations that all patients with Down's syndrome who wished to take part in sports involving stress on the head and neck in the special Olympic games should have a medical examination, and radiographs of the cervical spine taken in full flexion and extension, to ensure that there was no evidence of atlantoaxial subluxation or neurological abnormality. If these were both normal at 5–6 years of age no further follow up would be required.[11]

In Britain these recommendations were supported by the Department of Health and by Mencap,[12] [13] and so a radiograph of the neck indicating an abnormality led to restriction of active sports such as gymnastics, trampolining and diving, and to referral for neurological assessment.

Patients and methods

Between August 1973 and August 1980 the Hester Adrian Research Centre (HARC) recruited a cohort of children with Down's syndrome in the Greater Manchester area. They were referred by general practitioners, paediatricians, and health visitors. All diagnoses were confirmed by chromosomal analysis. The validity of this cohort was confirmed by notifications of Down's syndrome to the Office of Population Censuses and Surveys and from records at the regional cytogenetics laboratory.[14]

Of the 180 children in the cohort, 135 were admitted to the present study, 19 of the nonparticipants had died, 17 had moved from the area, and parental consent was refused in nine.

The children were aged between 6–14 years at the time of the study, mean 9·3 years. Ethics committee approval was granted. Informed consent was obtained and, for those families who agreed to take part, a letter was sent from the regional department of child and adolescent neurology to arrange a consultation. All the children were examined by one paediatrician (KAS) and the clinical findings were kept from the clinician interpreting the radiographs. The families were interviewed and a questionnaire with symptoms relating to neck stiffness, bowel and bladder control, toe walking, and sleep apnoea was discussed. Motor skills were assessed by the modified Gubbay test,[15] which consists of four independent tests scored against standardised norms for both normal children and children with moderate learning difficulties.[16]

Further assessments of hand and leg function and of gait were made with the quick neurological screening test.[17] Neurological examination included assessment of power, tone, reflexes, clonus, gait, and neck movements. The scoring of gait paid particular attention to eversion of the feet, abnormality of heel-toe placing, and fluency of movement.

The children then had radiographs of the cervical spine taken in flexed, extended, and neutral positions. Atlantoaxial distance was defined as the measurement from the posteroinferior aspect of the anterior arch of the atlas to the anterior surface of the odontoid process and was regarded as abnormal if it was >4·5 mm. All radiographs were reported by one consultant paediatric radiologist who was unaware of the clinical findings.

During the study, it was noted that a second radiograph of a child failed to show a previously observed abnormality. After this, the remaining 19 children in the study had repeat radiographs taken (with informed parental consent) after a 10 minute interval to indicate the degree of reliability.

The χ^2 test with Yates's correction was used to assess the significance of differences between groups, and a p value of <0·05 was accepted as significant. Relative risks and 95% confidence intervals (CI) were calculated.

Results

RADIOGRAPHS OF THE CERVICAL SPINE (table 1)
Most abnormalities were found in flexion, which identified 95% of patients with atlantoaxial subluxation.

Table 1 Abnormality (atlantoaxial distance >4·5 mm) shown on radiographs of the cervical spine in 19/135 patients

Position	*No (%) with abnormality*
Flexion (n=124)	18(15)
Extension (n=122)	12 (10)
Neutral (n=112)	11 (10)

NEUROLOGICAL ASSESSMENT (table 2)
Significantly more children with an abnormal gait had abnormal radiographs (nine of 30 compared with nine of 101, p<0·01). The relative risk of an abnormal radiograph of the neck occurring in a patient with an abnormal gait is 2·91 p<0·05, 95% CI 1 to 8). No other significant correlations were found. The gait measurements in the quick neurological screening test showed a positive but not significant correlation with abnormal radiographs of the neck (p=0·2). The sensitivity of gait as a measure of atlantoaxial subluxation was 50% and the specificity 81%.

The sequential set of results shown in table 3 are those of case 80, a 10 year old boy with evidence of toe walking. A further 18 children also had repeat radiographs. Of these 19 children (table 4) six (32%) showed an abnormality. In five this was in the first set of films, in four in the second, and in three in both sets. Only one of three (case 3) in the neutral position was recorded as abnormal in both radiographs. One of five (case 6) remained abnormal in flexion, and one of three (case 4) remained abnormal in extension.

Table 2 Correlation of radiographic appearance and gait in 131 children with Down's syndrome

Gait	*Radiographs*		*Total*
	No (%) normal	*No (%) abnormal*	
Normal	92 (91)	9 (9)	101
Abnormal	21 (70)	9 (30)	30

Four children with abnormal gait did not have radiographs taken.

Table 3 Atlantoaxial distance (mm) in three sets of radiographs on one patient

Position	*Radiograph*		
	1	*2*	*3*
Flexion	10	6	3
Extension	3	4	3
Neutral	12	2	5

Interval between radiographs 1 and 2 was three weeks and between radiographs 2 and 3 was 10 minutes.

Table 4 Atlantoaxial distances (mm) on two sets of radiographs taken 10 minutes apart from six of 19 children with radiographic abnormalities

Case No	*Position*					
	Neutral		*Flexion*		*Extension*	
	First	*Second*	*First*	*Second*	*First*	*Second*
1	Not recorded	4	2	5	4	3
2	Not recorded	2	7	3	4·5	3
3	4·5	4·5	4	4	3	3
4	3	3	3	5	5	5
5	5	3	5	3	5	2·5
6	12	2	10	6	3	4

Discussion

The high incidence of atlantoaxial subluxation in Down's syndrome has been widely reported,[1–10] and our incidence of 14% is in keeping with those results. Abnormalities of the odontoid process including hypoplasia and accessory odontoid ossicles have been reported relatively frequently in other studies.[8] The methods on which the radiographic abnormalities are based refer almost exclusively to the adult population, and as the odontoid peg (which has four ossification centres that ossify at various stages and then fuse together) does not attain its normal size and shape until at least 8–10 years of age, it will look relatively 'hypoplastic' in normal children. We did not identify any specific abnormality of the odontoid peg.

This study was carried out in a cohort of children with Down's syndrome. To our knowledge this is the first such study, and as it is a population based study it is reliable.

Radiographs of the neck seem to be unreliable in identifying atlantoaxial subluxation (the observed 14% abnormality had a 95% CI of 0 to 25). The reason for the variability may be due to ligamentous laxity; it cannot be due to upper respiratory tract infections[20] or any other anomaly of the cervical vertebrae.[8]

Subjective observers have noted alterations in muscle tone with mood in children with Down's syndrome (hypotonic when subdued compared with relatively normal when angry or excited), and this may contribute to the lack of reliability of radiographs.

Almost all the cases of atlantoaxial dislocation that have been reported were preceded by abnormal neurological symptoms and signs,[18 19] and Pueschel found a 1·5% incidence of neurological signs with neck abnormalities.[5] All the children in our study with radiographic abnormalities were asymptomatic with no neurological signs.

We attempted to assess predictive signs of atlantoaxial subluxation—objective measurements of gait abnormalities were not significantly associated with neck abnormalities. Further study of qualitative measures of gait in community based paediatric practice would be of value.

As radiographs of the neck are unreliable at identifying atlantoaxial subluxation we cannot recommend them for screening. Although the sensitivity of gait abnormality with a neck radiograph abnormality was 50% this may not be the result of pyramidal tract dysfunction, but of the hypotonia seen in the neck and feet of children with Down's syndrome.

Bearing in mind the extreme rarity of cord compression reported in the world literature, and given the poor reliability and reproducibility of abnormal radiography of the neck, we think that many children with Down's syndrome are having their lives unnecessarily restricted by defensive medical practice. Our findings would support the view of a re-examination of the evidence reported by Davidson in 1988.[21] He, together with Roy *et al*, stated that the widespread implication of screening would deprive individuals with Down's syndrome from beneficial activities. In view of the above findings we feel that the advice given by Department of Health should be revised.

We thank Professor Cliff Cunningham for his advice and support and for information about the original cohort.

1 Pueschel SM, Scola FH. Epidemiological radiographic and clinical studies of atlantoaxial instability in individuals with Down's syndrome. *Pediatrics* 1987;**80**:555–60.

2 Pueschel SM, Scola FH, Perry CD, *et al*. Atlantoaxial instability in children with Down's syndrome. *Pediatr Radiol* 1981;**10**:129–32.

3 Martel W, Tischler JM. Observation on the spine in mongolism. *AJR* 1966;**94**:630–8.

4 Tischler JM, Martel W. Dislocation of the atlas in mongolism. Preliminary report. *Radiology* 1965;**84**:904–6.

5 Pueschel SM. Atlantoaxial subluxation in Down's syndrome. *Lancet* 1983;**i**:980.

6 Pueschel SM. Atlanto-axial instability. Sport and Down's syndrome. *Lancet* 1989;**i**:438–9.

7 Spitzer R, Rabinovitch JY, Wyber KC. A study of abnormalities of the skull, teeth and lenses in mongolism. *Can Med Assoc J* 1961;**84**:567–72.

8 Elliott S, Morton RE, Whitelaw RAJ. Atlantoaxial instability and abnormalities of the odontoid in Down's syndrome. *Arch Dis Child* 1988;**63**:1484–9.

9 Roy M, Baxter M, Roy A. Atlanto instability in Down's syndrome—guidelines for screening and detection. *J R Soc Med* 1990;**83**:433–5.

10 Semine AA, Ertel AN, Goldberg MJ, Bull MJ. Cervical spine instability in children with Down's syndrome. *J Bone Joint Surg [Am]* 1978;**60**:649–52.

11 American Academy of Pediatrics. Committee on sports medicine. Atlantoaxial instability in Down's syndrome. *Pediatrics* 1984;**74**:152–4.

12 Acheson ED. *Atlantoaxial instability in people with Down's syndrome*. London: DHSS, 1986. (CMO (86) 8.)

13 Royal Society for Mentally Handicapped Adults and Children. *Look before you leap. Sports and people with Down's syndrome*. London: Mencap, 1985.

14 Cunningham C. Early support and intervention. The Hester Adrian Research Centre infant project. In: Mittler PJ, McConachie HR, eds. *Parents, professionals and mentally handicapped people: approaches to partnership*. London: Croom Helm, 1983.

15 Gubbay SS. The mangement of developmental apraxia. *Dev Med Child Neurol* 1978;**20**:643–6.

16 McKinlay I, Bradley G, Hindle A, Ehrhardt P. Motor coordination of children with mild mental handicap. *Ups J Med Sci* 1987;(suppl):127.

17 Mutti M, Sterling HM, Spalding NV. *Quick neurological screening test—revised edition*. Academic therapeutic publication. San Jose: State University, 1978.

18 Choudry V, Sturgeon C, Gates AJ. Symptomatic atlantoaxial dislocation in Down's syndrome. *Ann Neurol* 1978;**21**:606–9.

19 Hungerford GD, Akkaraya V, Rowe SE, Young GF. Atlanto-occipital and atlantoaxial dislocation with spinal cord compression. A case report and review of the literature. *Br J Radiol* 1981;**54**:758–61.

20 Coria F, Quintana F, Villaba M. Craniocervical abnormalities in Down's syndrome. *Dev Med Child Neurol* 1983;**25**:252–5.

21 Davidson RG. Atlantoaxial instability in individuals with Down's syndrome: a fresh look at the evidence. *Pediatrics* 1988;**81**:857–65.

Archives of Disease in Childhood 1991; **66**: 879–882

Subcutaneous or intramuscular insulin injections

C P Smith, M A Sargent, B P M Wilson, D A Price

Abstract

To find out whether diabetic children may inject their insulin intramuscularly rather than subcutaneously, a random sample of 32 patients aged 4·3–17·9 (median 11·3) years was studied. Distance from skin to muscle fascia was measured by ultrasonography at standard injection sites on the outer arm, anterior and lateral thigh, abdomen, buttock, and calf. Distances were greater in girls (n=15) than in boys (n=17). Whereas in most boys the distances were less than the length of the needle (12·5 mm) at all sites except the buttock, in most girls, the distances were greater than 12·5 mm except over the calf. Over the fascial plane just lateral to the rectus muscle the distance from skin to peritoneum was less than 12·5 mm in 14 of the 17 boys and one of the 15 girls. Twenty five of the 32 children injected at an angle of 90°, and 24 children raised a skinfold before injecting. By raising a skinfold over the anterior thigh, the distance from skin to muscle fascia was increased by 19% (range 0–38%).

We conclude that most boys and some girls who use the perpendicular injection technique may often inject insulin into muscle, and perhaps on occasions into the peritoneal cavity.

For many years diabetic patients were advised to inject insulin into a skinfold, inserting the needle at an angle of 45°. Since the introduction of disposable plastic insulin syringes, which have much shorter (12·5 mm) needles, the recommended injection technique was altered. Most patients were advised to insert the needle at an angle of about 90° to nearly its whole length. To obtain a painless injection they were advised to stretch the skin before injecting, although thin patients were sometimes advised to raise a skinfold.[1] In this way it was felt that insulin would consistently be deposited into subcutaneous adipose tissue and the risk of penetrating muscle was considered to be negligible.

Frid and Linden were the first to cast doubt on the latter assumption when they showed by computed tomography that the depth of subcutaneous fat over many sites in the thigh and abdomen was often less than 10 mm in lean adult patients.[2] Their results were confirmed in a more recent report which showed by ultrasonography that the depth of subcutaneous fat over the deltoid muscle and the abdomen was less than 10 mm in 11 of 13 adult male volunteers.[3] These results suggest that adults who use the perpendicular injection technique may sometimes deposit insulin into muscle rather than fat.

Intermittent intramuscular administration of insulin could lead to variations in glycaemic control if the rate of absorption from muscle differed from that of the subcutaneous tissue. Recent studies in which modern imaging techniques were used to ensure accurate placement of insulin, have shown that insulin tends to be absorbed much faster from muscle than from subcutaneous adipose tissue.[3 4]

To assess the risk of inadvertent intramuscular injection of insulin in children of different ages and stages of development, we measured the distance from skin to muscle fascia at recommended injection sites by high resolution real time ultrasonography.

Patients and methods

A random sample of 32 diabetic children was recruited from the paediatric diabetic clinic at this hospital. All the subjects were white, except one who was Afro-Caribbean. Details of the insulin injection technique, sites used, and whether parent or child gave the insulin were recorded for each child. Injection sites were examined for areas of lipohypertrophy or lipoatrophy. All subjects were weighed, and height was measured with a Harpenden stadiometer. Percentage body mass index was used as a measure of the relative body weight of subjects,[5] and was calculated as: A/B×100% where A= actual weight/(actual height)^2 and B=50th centile weight for age/(50th centile height for age)^2. Weight and height were measured in kilograms and metres respectively. Subjects were examined to assess the stage of pubertal development using Tanner's criteria and were divided into prepubertal (stage 1) and pubertal (stages 2–5) groups.[6]

The glycated haemoglobin (bA$_1$) (HbA$_1$) measurement from the most recent clinic attendance (within three months) was recorded as an index of glycaemic control. Clinical details of subjects are shown in table 1. One prepubertal girl was included who was a newly diagnosed diabetic patient. She had a short history, was well, and had not lost weight. Her body mass index (108%) did not differ from the group as a whole.

Distances from skin to muscle fascia were measured with high resolution real time ultrasonography with an electronically focused 5MHz linear array transducer (Ultramark 9), and the accuracy of linear depth measurement was within 0·5 mm. The same investigator (MAS) made all measurements, and patients lay supine

Booth Hall
Children's Hospital,
Blackley,
Manchester M9 2AA
Department of
Paediatrics
C P Smith
D A Price

Department of Radiology
M A Sargent
B P M Wilson

Correspondence to:
Dr Smith.

Accepted 19 February 1991

Table 1 Clinical characteristics of study subjects. Results are expressed as median (range)

	Boys		*Girls*	
	Tanner stage 1 (n=9)	*Tanner stage 2–5 (n=8)*	*Tanner stage 1 (n=7)*	*Tanner stage 2–5 (n=8)*
Age (years)	9·2 (4·3–11·6)	15·3 (12·1–17·9)	9·1 (4·9–11·5)	14·5 (9·7–15·6)
Duration of diabetes (years)	4·8 (1–7·3)	5·7 (2·1–9)	2·6 (0–7·9)	4·2 (1·2–10·9)
% Body mass index	108* (103–120)	98* (93–125)	107 (79–121)	108 (96–132)
Glycated haemoglobin (%)	9·8 (8·4–11·3)	10·3 (7·8–14·1)	8·8 (8·6–11·9)	9·8 (7·5–14·3)

*p=0·02.

and prone during the study. Measurements at all sites were made in the transverse plane. Compression of the skin and underlying tissues was avoided during measurement by applying a layer of aqueous ultrasonic contact gel as a short transducer standoff device. By viewing the real time image it was possible to obtain measurements when there was no compression of skin or underlying tissues.

The within investigator variability was calculated from 10 measurements of uncompressed distance from skin to muscle fascia at the same site (anterior thigh) in the same subject. The results were concealed from the investigator by covering the figures at the bottom of the screen. The coefficient of variation for these measurements was 3·3%.

The distances from skin to muscle fascia were measured at the following sites, on the left hand side of the body:

(i) Outer arm—the lateral aspect of the arm one third of the way between the acromion of the scapula and the head of the radius.

(ii) Anterior thigh—the anterior aspect of the thigh in the midline halfway between the anterior superior iliac spine and the superior aspect of the patella. Measurements were repeated at this site with the skin squeezed in the way that some patients prepared for injection. Further measurements were then taken at the same site while pressing with the ultrasound transducer with sufficient pressure to cause maximum compression or displacement of underlying tissues.

(iii) Lateral thigh—the lateral aspect of the thigh halfway between the anterior superior iliac spine and the superior aspect of the patella.

(iv) Anterior abdomen—anterior to the thickest part of rectus muscle halfway between the anterior superior iliac spine and the umbilicus.

(v) Lateral abdomen (to peritoneum)—the distance from skin to peritoneum was measured lateral to the rectus muscle over the aponeuroses of the other abdominal muscles halfway between the anterior superior iliac spine and the umbilicus.

(vi) Buttock—the point in the centre of the upper outer quadrant of the buttock.

(vii) Calf—the posterior aspect of the calf in the midline halfway between the medial malleolus and the medial condyle of the tibia.

All subjects or their parents, or both, gave written informed consent, and the study was approved by the local ethics committee.

STATISTICAL ANALYSIS

Median values and ranges are given because data were not normally distributed. The Mann-Whitney U test was used to analyse the significance of differences. A probability of <0·05 was accepted as significant.

Results

PATIENTS

The median ages (range) of boys and girls did not differ: boys 11·6 years (4·3–17·9), girls 11·2 years (4·9–15·6). Median percentage body mass index was also similar (boys—105% (93–125), girls—107% (79–132)), but pubertal boys were leaner than prepubertal boys (p=0·02) (table 1).

INSULIN INJECTIONS

Insulin injections were administered by parent (10/32), child (14/32), or both parties (8/32). Numbers of sites used were: one, 6/32; two, 16/32; more than two, 10/32 children. Sites used were thigh (29/32), arm (22/32), abdomen (4/32), buttock (13/32), and calf (2/32). Inquiry about injection technique revealed that 24/32 children raised a skinfold before inserting the needle, 3/32 did not, and 5/32 did so on occasions. The needle was inserted at 90° by 25/32 children. The remainder injected at various angles between 45 and 90°. Twenty nine of 32 children reported that the needle was inserted as far as the hub.

INJECTION SITES

Six children had lipohypertrophy, but in no case was it evident at the site of measurement.

Distances from skin to muscle fascia (uncompressed)

Figures 1 and 2 show distances from skin to

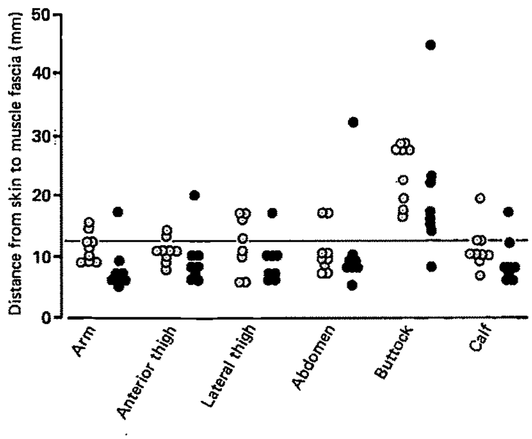


Figure 1 Distance from skin to muscle fascia at injection sites in prepubertal (○) and pubertal (●) boys. Horizontal line at 12·5 mm indicates length of needle. Distances were significantly greater in prepubertal boys over the arm (p=0·02) and anterior thigh (p=0·05).

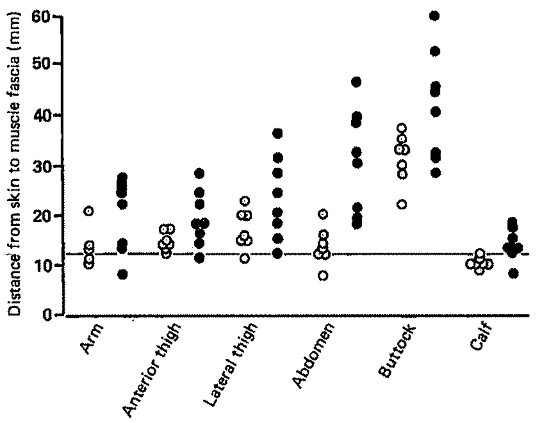


Figure 2 Distance from skin to muscle fascia at injection sites in prepubertal (○) and pubertal (●) girls. Horizontal line at 12·5 mm indicates length of needle. Distances were significantly less in prepubertal girls over the abdomen (p=0·003) and calf (p=0·02). Two girls were not included in the arm measurements as the results were technically unsatisfactory.

muscle fascia at the sites mentioned in boys and girls, respectively.

The most striking observation was that distances from skin to muscle fascia were much greater in girls than in boys; $p=0{\cdot}03$ for the calf, $p<0{\cdot}001$ for all other sites. In most boys the distance from skin to muscle fascia was less than 12·5 mm at all sites except the buttock. In contrast, most girls had subcutaneous fat layers of greater than 12·5 mm except over the calf, where prepubertal girls had little subcutaneous fat. The sex differences were most pronounced in pubertal children, girls having more subcutaneous fat than boys at all sites ($p<0{\cdot}02$). Prepubertal girls, however, also tended to have more subcutaneous fat than their male counterparts, but the differences were significant only over the anterior thigh and the buttock ($p<0{\cdot}01$).

When prepubertal and pubertal groups were compared, distances from skin to muscle fascia tended to be greater in girls during puberty rather than before, but were significant only over the abdomen ($p=0{\cdot}003$) and the calf ($p=0{\cdot}02$). In contrast, pubertal boys tended to have less subcutaneous fat over injection sites than prepubertal boys, and the differences were significant over the arm ($p=0{\cdot}02$) and the anterior thigh ($p=0{\cdot}05$).

Distances from skin to muscle fascia over raised skinfold

After the standard measurement over the anterior thigh had been made, a skinfold was raised and the measurement was repeated at the same site. Median values (range) for distances from skin to muscle fascia over the anterior thigh were 13 (6–28) mm and 15 (6–32) mm before and while squeezing the skin, respectively. The distance from skin to muscle fascia was increased by 3 mm (0–5 mm) when a skinfold was raised, a change of 19% (0–38%).

Distance from skin to peritoneum over lateral abdomen

Just lateral to the rectus muscle is an area about 2 mm wide that consists of skin, subcutaneous fat, and the aponeuroses of the abdominal muscles that converge to form the rectus sheath. Being devoid of muscle, the distance from skin to peritoneum is remarkably short, and is less than the length of the needle in most prepubertal and pubertal boys (table 2).

Table 2 Distance (mm) from skin to peritoneum just lateral to left rectus muscle, half way between the anterior superior iliac spine and the umbilicus

	Median (range)	*No in whom distance <12·5 mm*
Prepubertal boys (n=9)	11 (8–13)	7
Pubertal boys (n=8)	10 (8–38)	7
Prepubertal girls (n=7)	14 (7–20)	1
Pubertal girls (n=8)	31 (20–49)	0

Distances from skin to muscle fascia (compressed)

Additional measurements were taken over the anterior thigh while pressing with the ultrasound transducer with sufficient force to cause maximum compression or displacement of underlying tissues, as seen on the real time image. A comparison of these with measurements of uncompressed tissue at the same site showed that distances from skin to muscle fascia were reduced by 33% (17–45%) as a result of pressure. This reduction emphasises the importance of avoiding contact between transducer and skin during measurements.

Discussion

The present study shows that girls have a deeper subcutaneous fat layer than age matched boys over all standard sites for insulin injection. In girls the subcutaneous fat layer tends to be deeper during puberty rather than before, whereas in boys the reverse is true. These observations are consistent with the findings of Tanner and Whitehouse.[7] They reported a steady increase in skinfold measurements from the age of about 6 years to maturity in girls, whereas the increase was much less pronounced in boys, with a slight reduction in skinfold measurements during the period corresponding to the pubertal growth spurt. The difference in the subcutaneous fat layer between prepubertal and pubertal boys may have been exaggerated in the present study because the relative percentage body mass index was greater in prepubertal than in pubertal boys.

We found that in most boys the distance from skin to muscle fascia was less than the length of the needle (12·5 mm) at all sites except the buttock. In contrast, most girls had subcutaneous fat layers of more than 12·5 mm at all sites except the calf. Our findings in girls are perhaps surprising in view of the results from studies in adults. Frid and Linden showed that subcutaneous fat in the thigh and abdomen was often less than 10 mm thick in 14 non-obese adults, three of whom were female.[2] In contrast, another study showed that the majority of 10 non-obese patients (six female) had subcutaneous fat layers more than 12 mm thick over the upper medial thigh and the abdomen.[4] Both these studies measured the depth of subcutaneous fat with computed tomography whereas other investigators have used ultrasonography.[3 8] Vaag *et al* found that the overall mean thickness of the subcutaneous fat layer in the anterolateral aspect of the thigh was 4 (range 2–10) mm in lean men, and 7 (range 2–13) in lean women.[8] All these studies were of relatively small numbers of adult subjects who had all been selected because they were not obese. It is therefore impossible to estimate the risk of accidental intramuscular injections of insulin within a clinic population of diabetic adults from these data. Our results suggest that in children, most boys and some girls who do not raise a skinfold and who use the perpendicular injection technique deposit insulin in muscle rather than fat. Furthermore, it suggests that both sexes are at risk of accidental intramuscular injections of insulin when using the calves as the site of injection.

In the present study we investigated a random sample of children who attended a paediatric diabetic clinic. Twenty five of the 32 children used the perpendicular injection technique and in 24 the insulin was injected into a skinfold. Our results showed that by raising a skinfold the distance from skin to muscle fascia at the apex of the skinfold was increased by 3 (range 0–5) mm over the anterior thigh. It therefore seemed that most children, perhaps unwittingly, had adopted a sensible practice that increased the chance of insulin being deposited in fat rather than muscle. Our measurements, at the apex of the skinfold, took no account of the fact that some children inject into the down slope of a raised skinfold. This could further increase the chance of insulin being deposited in fat rather than in muscle.

Considering the abdomen as a site for injection, we were surprised to find that in the fascial plane lateral to the rectus muscle the distance from skin to peritoneum was less than the length of the needle in most boys and in a few girls. Although this fascial plane is only 2 mm wide it runs along the whole length of the rectus muscle, and its position makes it a relatively popular area for injection. It is therefore possible that insulin is occasionally given into the peritoneal cavity instead of the subcutaneous fat. We presume that absorption from the peritoneal cavity is faster than from subcutaneous tissues, and intraperitoneal insulin would have the theoretical advantage of presumably being absorbed into the portal circulation.

To compare absorption rates of subcutaneous and intramuscular insulin we have confined our review of publications to those studies that were controlled for depth of injection by direct measurement of subcutaneous tissue. One study showed a 50% higher rate of absorption of soluble insulin from an injection into a superficial thigh muscle compared with injection into a subcutaneous site, but no such difference was found with injections into these two types of tissue in the abdominal wall.[4] Another study compared rates of absorption of soluble insulin from subcutaneous, superficial, and deep intramuscular sites, and even superficial intramuscular injections resulted in more rapid absorption of insulin than subcutaneous injections.[3] In contrast, rates of absorption of soluble insulin from superficial and deep subcutaneous fat were similar.[9]

Vaag *et al* examined the metabolic consequences of intramuscular compared with subcutaneously administered insulin.[8] They found that insulin given intramuscularly before meals resulted in a more physiological profile of plasma-free insulin and a more stable blood glucose profile than subcutaneous administration. They also found pronounced differences in intramuscular absorption rates during rest and light physical activity, however, which were not evident after subcutaneous administration. This seems to be a serious disadvantage which should deter us, perhaps, from recommending the intramuscular route.

As a result of the present study and the review of publications, we plan to alter our recommendations for insulin injection in children. We suggest that insulin should be injected either at an angle of 45° into the apex of a skinfold,[10] or alternatively that it should be injected perpendicularly into the down slope of the skinfold. Furthermore, to try to ensure an adequate basal insulin supply overnight, we advise using the buttocks or thighs for the evening injection because absorption of insulin from these sites is slower than from the abdomen or arm.[11 12] At other times we suggest using a single anatomical region for injections to reduce day to day variation in absorption of insulin.[13] Lastly, we suggest that the calf is not a good site for injection in children because there is insufficient subcutaneous fat, and because we often had difficulty in raising a suitable skinfold over the calf when examining the children.

1 Watkins PJ. Insulin treatment. *BMJ* 1982;**284**:1929–32.

2 Frid A, Linden B. Where do lean diabetics inject their insulin? A study using computed tomography. *BMJ* 1986; **292**:1638.

3 Spraul M, Chantelau E, Koumoulidou J, Berger M. Subcutaneous or nonsubcutaneous injection of insulin. *Diabetes Care* 1988;**11**:733–6.

4 Frid A, Gunnarsson R, Guntner P, Linde B. Effects of accidental intramuscular injection on insulin absorption in IDDM. *Diabetes Care* 1988;**11**:41–5.

5 Cole TJ. A method for assessing age-standardized weight-for-height in children seen cross-sectionally. *Ann Hum Biol* 1979;**6**:249–68.

6 Tanner JM. *Growth at adolescence.* 2nd Ed. Oxford: Blackwell 1962.

7 Tanner JM, Whitehouse RH. Revised standards for triceps and subscapular skinfolds for British children. *Arch Dis Child* 1975;**50**:142–5.

8 Vaag A, Damgaard Pedersen K, Lauritzen M, Hildebrandt P, Beck-Nielsen H. Intramuscular versus subcutaneous injection of unmodified insulin: consequences for blood glucose control in patients with type 1 diabetes mellitus. *Diabetic Med* 1990;**7**:335–42.

9 Meijer PHEM de, Lutterman JA, van Lier HJJ, van't Laar A. The variability of the absorption of subcutaneously injected insulin: effect of injection technique and relation with brittleness. *Diabetic Med* 1990;**7**:499–505.

10 Thow J, Home P. Insulin injection technique. Depth of injection is important. *BMJ* 1990;**301**:3–4.

11 Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL. Factors influencing the absorption, serum insulin concentration, and blood glucose responses after injections of regular insulin and various insulin mixtures. *Diabetes Care* 1981;**4**:366–76.

12 Koivisto VA, Felig PH. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. *Ann Intern Med* 1980;**92**: 59–61.

13 Bantle JP, Weber MS, Rao SMS, Chattopadhyay MK, Robertson RP. Rotation of the anatomic regions used for insulin injections and day-to-day variability of plasma glucose in type I diabetic subjects. *JAMA* 1990;**263**: 1802–6.

Cytomegalovirus ileitis presenting as massive rectal bleeding in infancy

Boniface Kawimbe, Chris Bem, Prahlad Shripad Patil, Hoshang Bharucha

Department of Surgery,
University Teaching
Hospital,
PO Box 50110,
Lusaka,
Zambia
Boniface Kawimbe
Chris Bem
Prahlad Shripad Patil

The Queen's University,
Belfast,
Northern Ireland
Hoshang Bharucha

Correspondence to:
Mr Bem.

Accepted 28 February 1991

(*Arch Dis Child* 1991;**66**:883–884)

Abstract

Two Zambian infants presented with massive rectal bleeding caused by cytomegalovirus ileitis. The first was seropositive for HIV and the second seronegative, though her mother was seropositive. Both infants died.

Clinical infection with cytomegalovirus is uncommon in the general population, though it is often found in association with HIV infection.[1] We report two cases of cytomegalovirus enteritis that presented to the paediatric surgical department at the University Teaching Hospital, Lusaka, Zambia, during 1989.

Case reports

CASE 1

A 3 month old boy presented with a one day history of bloody diarrhoea. He had previously been in good health. On examination he was pale with a tachycardia of 152 beats/minute. The abdomen was soft and non-tender with hyperactive bowel sounds. There was a large quantity of blood clots on the nappy. Rectal examination confirmed the presence of blood. A provisional diagnosis of typhoid fever was made and in view of the life threatening haemorrhage laparotomy was done as soon as he had been resuscitated. The colon and terminal ileum were loaded with blood and the entire small bowel was covered in transmural plaque-like lesions, the heaviest concentration being in the terminal ileum. The terminal 20 cm of ileum were resected and intestinal continuity restored by ileocaecal anastomosis. When the resected bowel was opened the plaque-like lesions were seen to be ulcerations of varying depth. Postoperatively the infant developed a coagulopathy and wound infection, and (on the tenth day) peritonitis. At the second laparotomy multiple perforations in the remaining part of the small intestine were found and he died a few hours later. The child was seropositive for HIV (Wellcozyme recombinant).

CASE 2

A 6 month old previously healthy girl presented with a three day history of coughing, vomiting, and bloody diarrhoea. On examination she was pale and had a tachycardia of 124 beats/minute. Her chest was normal. The abdomen was soft and non-tender with normal bowel sounds. Blood was found on rectal examination, and a provisional diagnosis of intussusception made. At laparotomy the terminal ileum and colon were filled with blood and there were plaque-like lesions similar to those in case 1, but not as florid. A 30 cm length of terminal ileum was resected, with ileoileal anastomosis. The infant died two hours after laparotomy of hypovolaemic shock. She was seronegative for HIV, though her mother was seropositive (Wellcozyme recombinant).

In both cases permission for necropsy was refused. The surgical specimens showed round, oval transverse ulcers 0·5 to 1 cm in diameter and at different stages of evolution. Histopathological features included focal transmural inflammation rich in mononuclear cells. Fibroblasts and endothelial cells contained eosinophilic inclusions characteristic of cytomegalovirus infection. Gram, Ziehl-Neelsen, periodic acid Schiff, and Grocott-Gomori stains showed no abnormalities. Immunoperoxidase staining by the avidin biotin complex method (DAKO) confirmed the presence of cytomegalovirus. The primary antiserum used was a monoclonal anticytomegalovirus (DAKO-M757) at a dilution of 1:50 pretreated with trypsin.

Discussion

Cytomegalovirus is normally a common subclinical infection acquired at any time from intrauterine to late adult life. Clinical infection has become important as a sign of compromise of the immune system by HIV infection.[1]

The diagnosis of clinical infection can confidently be made if the characteristic inclusion bodies are found in biopsy material; immunohistological staining increases the sensitivity of histological examination.[2] The presence of cytomegalic inclusion bodies at the sites of ulceration and inflammation in the cases reported suggests strongly that cytomegalovirus was the pathogen directly responsible for causing the devastating clinical ileitis, though it has recently been postulated that in the presence of HIV infection cytomegalovirus may have only a secondary pathogenic role.[3]

There is no conclusive proof that the two patients were infected with HIV. Testing for HIV infection in infants by antibody detection lacks the specificity and sensitivity that it has in adults because of the presence of maternal antibodies.[4] Technically advanced methods for detecting the HIV antigen in the infants were not available, but such a remarkable presentation of an infection associated with HIV, the background prevalence of HIV infection in mothers delivering at the University Teaching Hospital, Lusaka,[5] and the positive Wellcozyme test in one infant and in the mother of the other, suggests that both children were immunocompromised despite their previously apparent good health.

Occasional reports of cytomegalovirus infection in immunocompromised children have been reported from elsewhere, including, one other case of life threatening gastrointestinal haemorrhage.[6] The cases reported here emphasise that particularly where there is the likelihood of HIV infection, cytomegalovirus enteritis must be considered in an infant presenting with rectal bleeding. It is unlikely that a definitive preoperative diagnosis will often be made, though a less acute presentation may permit time for mucosal biopsy.[2] Retinoscopy may help if coexisting cytomegalovirus chorioretinitis is present. At laparotomy the presence of widespread ulcerative lesions should alert the surgeon to the possibility of the diagnosis.

In both cases the clinical problem was one of exsanguinating haemorrhage, and at laparotomy

[redacted]

excised. In the first case the haemorrhage continued, and though the infant survived the initial operation he died of perforation of the remaining lesions, which indicated the progressive nature of the disease. If arteriography is available it could be used to localise the site of bleeding, thereby permitting the correct operation to be done and antiviral treatment to be given to control the infection.

1 Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988;**108**:585–94.

2 Culpepper-Morgan JA, Kotler DP, Scholes JV, Tierney AR. Evaluation of diagnostic criteria for mucosal cytomegalic inclusion disease in the acquired immune deficiency syndrome. *Am J Gastroenterol* 1987;**82**:1264–70.

3 Morris DJ. Is human immunodeficiency virus (HIV) rather than cytomegalovirus the cause of retinitis and colitis in HIV-infected patients? *Rev Infect Dis* 1990;**12**:557–9.

4 Mok J. HIV infection in children. *Br J Hosp Med* 1990;**43**: 247–51.

5 Hira SK, Kamange J, Bhat GJ, *et al*. Perinatal transmission of HIV-1 in Zambia. *BMJ* 1989;**299**:1250–2.

6 Schwartz DL, So HB, Bungarz WR, *et al*. A case of life-threatening gastrointestinal haemorrhage in an infant with

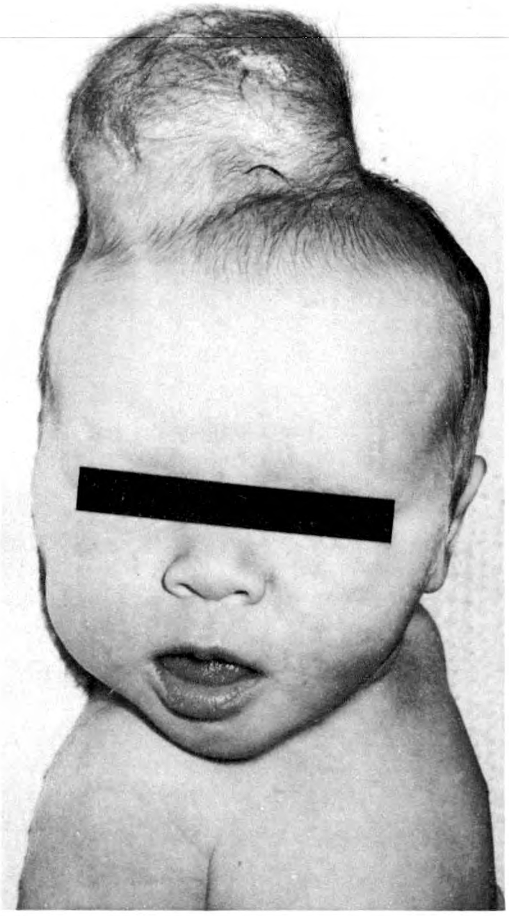


Figure 2 Case 2, aged 2 days.

The baby was delivered at term by caesarean section because his mother had undergone a previous section for cephalopelvic disproportion. At birth a solid, skin covered, lesion 5 cm in diameter was noted in the parietal region, it did not transilluminate. The anterior fontanelle was normal (fig 2).

Ultrasound examination showed a uniformly dense lesion with no intracranial extension and normal cerebral ventricles. At operation the tumour was easily excised, and histological examination showed dermatofibroma. There was no evidence of recurrence of the tumour five years later.

Discussion

Subcutaneous tumours commonly present at birth and in infancy.[1 2] In a survey of 120 congenital tumours, only two were solitary scalp tumours, one a 'fibroma', and the other a rhabdomyosarcoma. The two tumours reported here can probably be included in Enzinger's group of 'fibrous harmatoma of infancy', in which he reported a definite prevalence among boys.[2] These tumours can develop during infancy, or be present at birth. It is likely that the lesion in our second case developed after the 16th week of gestation, which would suggest that the initial α fetoprotein result was unimportant.

Encephaloceles arise as a result of failure of normal development of the neural tube, and so they lie in, or immediately adjacent to, the midline.[3] In both our patients the diagnosis of encephalocele was considered because of the proximity of the tumours to the midline. Tumours that are separate from the midline are unlikely to be encephaloceles. A further differentiating feature is that, in contrast to our second case, there is usually no hair over an encephalocele.[3]

The use of ultrasonography in case 2 provided a simple method of showing that the lesion was entirely extracranial; this is consistent with the experience of others who have investigated extracranial masses.[4]

1 Kauffman SI, Stout AP. Congenital mesenchymal tumours. *Cancer* 1965;**18**:460–76.
2 Enzinger FM. Fibrous hamartoma of infancy. *Cancer* 1965; **18**:241–8.
3 McLaurin RL. Parietal cephaloceles. *Neurology* 1964;**14**: 764–72.
4 Fisher AQ, Leibrock LG, Anderson JC. Evaluation of congenital extracranial masses by waterbath ultrasonography. *Pediatric Neurology* 1985;**1**:117–9.

Archives of Disease in Childhood 1991; 66: 886–889

CURRENT TOPICS

Epidemiology of hypochromic anaemia in young children

David Stevens

Paediatric Department, Gloucestershire Royal Hospital, Gloucester GL1 3NN

Correspondence to: Dr Stevens.

Evidence that iron deficiency affects the developmental progress and growth of young children[1 2] has drawn attention to the importance of treating children who are iron deficient, even when anaemia is mild, and has given a new impetus to study the prevalence of iron deficiency in this age group. However, there are a number of reasons why it is difficult to obtain accurate estimates of the prevalence of iron deficiency anaemia in young children. Studies of the epidemiology of childhood anaemia are hampered by the problem of the definition of anaemia, by an understandable reluctance to take blood tests from apparently healthy children, and by the difficulty in assessing the contribution of the three commonest causes of anaemia: iron deficiency, genetic factors, and infection. Serum ferritin estimations are a much better test of iron status than transferrin saturation, reflect body stores of iron,[3] can be performed on small amounts of blood, and are useful in clinical practice and in epidemiological studies. However serum ferritin and other tests of iron deficiency such as free erythrocyte protoporphyrin and transferrin saturation do not have well defined cut off values that exclude iron deficiency anaemia in young children,[4] and all these tests can show misleading results in the presence of infection.[5 6] A serum ferritin concentration below 10 μg/l is good evidence of iron deficiency,[7] but some young children with serum ferritin concentrations up to 30 μg/l show a rise of haemoglobin in response to iron therapy. Similar problems occur with other laboratory tests of iron deficiency.[4]

A therapeutic trial of iron is the only completely reliable way of excluding iron deficiency anaemia and although this is relatively easy in clinical practice, it presents major problems in epidemiological studies. Genetic anaemias can be difficult to exclude because α thalassaemia can only be reliably diagnosed by modern DNA techniques[8] and the anaemia of infection has to be diagnosed by indirect methods. Finally, in some children all three factors may be present and contribute to the pathogenesis of anaemia.

A report from the World Health Organisation (WHO),[9] using their own reference standards,[10] estimates that 12% of children under 5 years of age in the developed world and 51% in the developing world are anaemic. How common is anaemia in young children in Britain and is iron deficiency mainly responsible? The WHO define anaemia in this age group as a haemoglobin concentration below 110 g/l,[10] which is approximately 2SD below the mean for iron replete white children of this age group.[11] The reference range is therefore suitable for a healthy iron replete population with a very low frequency of genetic anaemia. It is important to recognise that some children with iron deficiency anaemia have haemoglobin concentrations above 110 g/l[12] and show a rise of haemoglobin with iron therapy to achieve their optimal haemoglobin and that some children with concentrations below 110 g/l are healthy and have no pathological cause for a low haemoglobin level. Despite these reservations the WHO definition is a good starting point to examine the prevalence and cause of anaemia in this group in Britain.

Iron deficiency

The prevalence of iron deficiency anaemia has decreased appreciably in young British children since Helen McKay's classic studies in central London in the 1920s.[13] Very few of the infants between 2 and 17 months of age in her study achieved a haemoglobin concentration of 110 g/l without iron supplements. This contrasts with 1971, when Burman reported that during the first two years of life the mean haemoglobin of Bristol infants who were not given iron supplements was similar to that of infants who were given iron in Mackay's study.[14] However iron deficiency anaemia remains common in inner city areas (table 1) where in one study Aukett *et al* found that 27% of Asian and 18% of European children had haemoglobin concentrations below 110 g/l.[2] Serum ferritin estimations and response to iron therapy showed that most of this anaemia was due to iron deficiency. Grindulis *et al* also found that anaemia was common in young Asian children and that 90% of those with haemoglobin concentrations below 100 g/l had serum ferritin below 7 μg/l.[16] Earley *et al* found that anaemia was commoner in Asian than European children but, surprisingly, low serum ferritin concentrations were commoner in the latter (personal communication).[17] However, serum ferritin proved to be an unreliable test of iron deficiency in this study. Burman's study[14] contained many middle class infants but recent studies including more affluent groups are scanty. Wright *et al* found that there was no significant difference in the proportion of affluent and deprived infants with haemoglobin concentrations below 110 g/l and remarked that the red cell indices were only

Table 1 Surveys of anaemia in young children

Author	*Location of study*	*Age (months)*	*Ethnic group*	*Anaemic* (%)*	*Low serum ferritin (%)*
Ehrhardt[15]	Bradford	6–48	European	12	28†
			Asian	28	45†
Grindulis *et al*[16]	Birmingham	21–23	Asian	31	57‡
Aukett *et al*[2]	Birmingham	17–19	European	18	47§
			Asian	27	
Earley *et al*[17]	London	6–72	European	10	35†
			Asian	27	13†
Mills[18]	London	8–24	European	17	nk‖
			Asian	26	
			Predominantly Caribbean	18	
Marder *et al*[19]	Nottingham	15–24	European	16	nk‖
			Asian	26	
			Caribbean	20	
Wright *et al*[20]	Newcastle	9–15	'Affluent'	11	nk‖
			'Deprived'	16	
James *et al*[21]	Bristol	12–48	European	4¶	Limited number of estimations
			Caribbean	8¶	
			Indian	17¶	
			Vietnamese	20¶	

*Haemoglobin concentration <110 g/l (exceptions indicated by ¶)
†Percentage of total sample with serum ferritin concentration <10 μg/l; ‡serum ferritin concentration <7 μg/l.
§Percentage of anaemic children with serum ferritin concentration <7 μg/l.
‖No biochemical tests of iron deficiency performed.
¶Haemoglobin concentration <105 g/l.

typical of iron deficiency anaemia in 3%.[20] The evidence suggests, however, that the prevalence of iron deficiency anaemia in young British children varies greatly according to social circumstances and nutritional habits but is unlikely to be less than 2–3% in any group and has been shown to be approaching 30% in the most disadvantaged.

The possibility of coeliac disease and occult blood loss must be considered in children with iron deficiency anaemia, particularly if the anaemia is recurrent, but the great majority of cases of iron deficiency anaemia in young children are due to a failure of nutritional iron to keep up with the demands of growth. Normal birthweight infants are born with sufficient body iron, mainly in the form of haemoglobin, to keep up with the demands of growth irrespective of their nutritional intake until about 4–6 months of age.[22] Low birthweight infants, however, are at risk of developing iron deficiency anaemia by 2 months of age if they are not given iron supplements.[23] After 4 to 6 months of age a number of nutritional factors may predispose the infant to developing iron deficiency.[7] Delayed introduction of solid feeds, feeds of low iron content or with poorly available iron, or feeds which inhibit iron absorption,[7] and ingestion of unmodified cows' milk[24 25] may all contribute. However, the relative importance of these factors in the pathogenesis of iron deficiency in young British children is not known.

Infection

Common infections such as otitis media and upper respiratory tract infection can depress haemoglobin concentrations in young children.[5 26] Even the mild infection produced by the attenuated measles vaccine can reduce haemoglobin in children.[27] As iron deficiency becomes less common in affluent societies infection will probably account for an increasing proportion of cases of mild anaemia in young children.[5 26] Repeated infections increase the severity of the anaemia and low haemoglobin concentrations can persist for one month after infections even in children who subsequently show no signs of illness.[5] In paediatric practice, persistent or repeated infections are a common reason why young children have a haemoglobin measured and are at the same time probably a much commoner cause of anaemia than was previously recognised.

Genetic factors

Sickle cell anaemia, thalassaemia, and glucose-6-phosphate dehydrogenase deficiency are all important causes of anaemia in racial groups originating from malarial areas and are therefore important in children of many of the ethnic minorities in Britain. Haemoglobin E is very common in some parts of South East Asia and also occurs in India.[28] Heterozygotes have normal haemoglobin concentrations with some microcytosis and hypochromia and homozygotes are not usually anaemic but the condition may interact with β thalassaemia to cause severe anaemia.[28] Mild forms of thalassaemia such as β thalassaemia trait and mild forms of α thalassaemia can both cause a hypochromic microcytic anaemia, are very common in some racial groups, and can easily be confused with iron deficiency anaemia. Heterozygotes for β thalassaemia have a mild asymptomatic hypochromic anaemia, the severity of which probably depends mainly on whether the affected person inherits the β^0 or β^+ type of β thalassaemia.[29] In a study of young children aged 1–3 years, heterozygous for β thalassaemia of unspecified type, 90% had haemoglobin concentrations between 90 and 106 g/l.[30] The proportion of carriers in different ethnic groups is difficult to determine from published work because the populations studied are in many cases small, there may be great variation within ethnic groups, and the diagnostic criteria also vary. The results of some studies are shown in table 2 but should not be regarded as comprehensive. The Indian subcontinent is genetically ex-

*Table 2 Distribution of thalassaemia in some ethnic groups**[8 28 31–34]

Ethnic group	β *Thalassaemia (carriers)**	α *Thalassaemia (frequency of* $-\alpha$)
Afro-Caribbean	0·8%	0·18
Indian	<1–~20%	0·05–0·9
Mediterranean	<1–~20%	0·04–0·18

*See text.

tremely heterogeneous and even within relatively small geographical areas the frequency of haemoglobinopathies can vary widely between different tribes, castes, and religious groups.[32]

α Thalassaemia results from reduction of α globin synthesis, either from a deletion of one or more of the four genes ($\alpha\alpha/\alpha\alpha$) which are responsible for α globin production, or as a result of 'non-deletional' abnormalities, which through a variety of mechanisms reduce α globin synthesis without gene deletion.[33] Severe forms of α thalassaemia, such as the double gene deletion variety ($--/$) and severe non-deletional forms are uncommon in the main ethnic minorities in Britain, which explains why the clinically significant forms of α thalassaemia, Bart's hydrops and haemoglobin H disease, are rarely seen. However the single α gene defect ($-\alpha$) is common in many parts of the world which have provided immigrants to British including the Caribbean, South East Asia, the Middle East, Indian subcontinent, and some Mediterranean countries.[33] Table 2 shows the frequency of the single α gene defect ($-\alpha$) in some ethnic groups. The frequency is extremely high in many of these groups resulting in very high percentages of the population having the defect. For example, from a frequency of 0·18 in Afro-Caribbeans it can be estimated that 33% have the defect (heterozygotes and homozygotes). At the present time accurate estimates of the frequency of α thalassaemia, based on DNA studies, are not yet available for the main immigrant groups from the Indian subcontinent.

Is α thalassaemia a common cause of hypochromic anaemia in children in the ethnic minorities in Britain? Although DNA studies indicate that the single α gene defect is likely to be present in thousands of children in the ethnic minorities, the effect on the overall prevalence of hypochromic anaemia may be quite limited. The single α gene defect is a very mild disorder. Homozygotes have a mild hypochromic anaemia and many of the heterozygotes have normal red cell indices.[33 34] Young Jamaican children, heterozygous for the single α gene defect, were found to have lower mean haemoglobin, mean corpuscular volume, and mean corpuscular haemoglobin than normal children but there was considerable overlap with normal children.[35] Epidemiological studies using modern DNA techniques have provided evidence that α thalassaemia of the single α gene defect type is a common cause of hypochromic anaemia in the Pacific islands of Vanuatu.[36] It may be responsible for much of the mild hypochromic anaemia previously thought to be due to iron deficiency in Bedouin infants in Saudi Arabia,[37] and is an important cause of microcytosis in Gujerati children in London.[17] In the latter study suspected iron deficiency was confirmed by therapeutic trial of iron,[17] but in the others the less reliable method of serum ferritin estimations was used.[36 37] The effect of iron deficiency may therefore have been underestimated. In clinical practice the single α gene form of α thalassaemia is probably an important cause of mild hypochromic anaemia and microcytosis persisting after iron therapy in children from the ethnic minorities.

Conclusion

It is clear that many young British children have haemoglobin concentrations which are low by WHO reference standards. Although other causes of hypochromic anaemia such as lead poisoning and renal failure are important to exclude if clinically indicated, iron deficiency, infection, and thalassaemia[26] are responsible for the vast majority of cases of mild anaemia (haemoglobin 100–110 g/l) in young children. All three types of anaemia can result in a hypochromic blood picture, although infection is more often associated with normochromic red cells. Iron deficiency, a preventable nutritional disorder, is still common in disadvantaged groups but the overall prevalence is unknown. Young Asian children living in inner city areas have the highest risk of developing iron deficiency anaemia but no ethnic group or social class is immune from this disorder. Dietary campaigns[38 39] have had success in preventing iron deficiency but more studies are needed to find out the best way to improve the diet of young children in order to prevent this condition, which is probably more harmful than we previously realised.

In clinical practice it is important to treat iron deficiency anaemia in young children. Clinical history, including that of recent infections, a few questions about the diet, and examination of the child and his blood film and/or red cell indices often leads to the correct diagnosis, but if there is any doubt a therapeutic trial of iron should be given and accompanied by dietary advice. This is very unlikely to cause harm even if the anaemia is due to a recent infection or thalassaemia trait. It is probably best to investigate for thalassaemia trait after iron deficiency has been corrected. Children whose haemoglobin concentration and red cell indices do not return to normal after a course of iron require investigation. Poor compliance, a persisting cause of iron deficiency, and other causes of anaemia should be considered. Children from the ethnic minorities who do not fully respond to iron should have haemoglobin electrophoresis performed, including haemoglobin (HbA_2) estimation to diagnose heterozygous β thalassaemia. If this is excluded and the child does not have any other cause of anaemia, and the serum ferritin concentration is normal, the most likely cause of mild persistent hypochromic anaemia and microcytosis is a mild form of α thalassaemia. Prolonged or repeated courses of iron should be avoided if the anaemia is due to thalassaemia.

I thank Dr D R Higgs and Professor B A Wharton for reading through this manuscript and making helpful suggestions.

1 Oski FA, Honig AS, Helm B, Howanitz P. Effect of iron therapy on behaviour performance in nonanemic iron deficient infants. *Pediatrics* 1983;**71**:877–80.
2 Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;**61**:849–59.
3 Jacobs A, Miller F, Wormwood M, Beamish MR, Waldrop CA. Ferritin in normal subjects and patients with iron deficiency and iron overload. *BMJ* 1972;**iv**:206–8.
4 Dallman PR, Reeves JD, Driggers DA, Lo EYT. Diagnosis of iron deficiency: the limitations of laboratory tests in predicting response to treatment in year-old infants. *J Pediatr* 1981;**98**:376–81.
5 Jansson LT, Kling S, Dallman PR. Anemia in children with acute infections seen in a primary care pediatric outpatient clinic. *Pediatr Infect Dis* 1986;**5**:424–7.
6 Elin RJ, Wolff SM, Finch CA. Effect of fever on serum iron and ferritin concentrates in man. *Blood* 1977;**49**:147–53.
7 Oski FA, Stockman JA. Anemia due to inadequate iron sources or poor iron utilisation. *Pediatr Clin North Am* 1980;**27**:237–52.
8 Weatherall DJ, Clegg JB. *The thalassaemia syndromes*. 3rd Ed. Oxford: Blackwell, 1981.
9 De Maeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. *World Health Stat Q* 1985;**38**:302–16.
10 World Health Organisation. Nutritional anaemias. *WHO Tech Rep Ser* 1972;No 503.
11 Dallman PR, Siimes MA. Percentile curves for hemoglobin and red cell volume in infancy and childhood. *J Pediatr* 1979;**94**:26–31.
12 Driggers DA, Reeves JD, Lo EYT, Dallman PR. Iron deficiency in one-year-old infants: comparison of results of a therapeutic trial in infants with anemia or low-normal hemoglobin. *J Pediatr* 1981;**98**:753–8.
13 MacKay HM. Anaemia in infancy: its prevalence and prevention. *Arch Dis Child* 1928;**3**:117–47.
14 Burman D. Haemoglobin levels in normal infants aged 3 to 24 months, and the effect of iron. *Arch Dis Child* 1972;**47**:261–71.
15 Ehrhardt P. Iron deficiency in young Bradford children from different ethnic groups. *BMJ* 1986;**292**:90–3.
16 Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child* 1986;**61**:843–8.
17 Earley A, Valman HB, Altman DG, Pippard MJ. Microcytosis, iron deficiency, and thalassaemia in preschool children. *Arch Dis Child* 1990;**65**:610–4.
18 Mills AF. Surveillance for anaemia: risk factors in patterns of milk intake. *Arch Dis Child* 1990;**65**:428–31.
19 Marder A, Nicoll A, Polnay L, Shulman CE. Discovering anaemia at child health clinics. *Arch Dis Child* 1990;**65**:892–4.
20 Wright CM, Reading RF, Halse PC, Watson JG. Iron deficiency in adolescents. *BMJ* 1989;**298**:1035–6.
21 James J, Evans J, Male P, Pallister C, Hendrikz JK, Oakhill A. Iron deficiency in inner city pre-school children: development of a general practice screening programme. *J R Coll Gen Pract* 1988;**38**:250–2.
22 Oski FA. Food for the red cell. In: Wharton BA, ed. *Nutrition in childhood. Topics in paediatrics* 2. Royal College of Physicians of London: Pitman Medical, 1980:132–50.
23 Lundstrom U, Siimes MA, Dallman PR. At what age does iron supplementation become necessary in low birth weight infants? *J Pediatr* 1977;**91**:878–83.
24 Tunnessen WW, Oski FA. Consequences of starting whole cow milk at 6 months of age. *J Pediatr* 1987;**111**:813–6.
25 Zeigler EE, Fomon SJ, Nelson SE, *et al*. Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. *J Pediatr* 1990;**116**:11–8.
26 Dallman PR. Changing characteristics of childhood anemia. *J Pediatr* 1989;**114**:161–4.
27 Olivares M, Walter T, Osorio M, Chahud P, Schleshinger L. Anemia of mild viral infection: the measles vaccine as a model. *Pediatrics* 1990;**84**:851–8.
28 Dacie JV. *The haemolytic anaemias. Vol 1. The hereditary haemolytic anaemias. Part 2*. 3rd Ed. London: Churchill Livingstone, 1988.
29 Millard DP, Mason K, Serjeant BE, Serjeant GR. Comparison of haematological features of the β^{o} and β^{+} thalassaemia traits in Jamaican negroes. *Br J Haematol* 1977;**36**:161–70.
30 Berman BW, Ritchey AK, Jekel JF, Schwartz AD, Guilliotis DK, Pearson HA. Hematology of β-thalassaemia trait—age related developmental aspects and intrafamilial correlations. *J Pediatr* 1980;**97**:901–5.
31 Serjeant GR, Serjeant BE, Forbes M, Hayes RJ, Higgs DR, Lehmann H. Haemoglobin gene frequencies in the Jamaican population: a study of 100,000 newborns. *Br J Haematol* 1986;**64**:253–62.
32 Brittenham GM. The geographic and ethnographic distribution of hemoglobinopathies in India. In: Bowman JE, ed. *Distribution and evolution of hemoglobin and globin loci.* Amsterdam: Elsevier Publishing Co, 1983:171–8.
33 Higgs DR, Vickers MA, Wilkie AOM, Pretorius IM, Jarman AP, Weatherall DJ. A review of the molecular genetics of the human α-globin gene cluster. *Blood* 1988;**73**:1081–104.
34 Higgs DR, Weatherall DJ. Alpha-thalassaemia. *Current Topics in Hematology* 1983;**4**:37–97.
35 Maude GH, Higgs DR, Beckford M, *et al*. Alpha thalassaemia and the haematology of normal Jamaican children. *Clin Lab Haematol* 1985;**7**:289–95.
36 Bowden DK, Hill AVS, Higgs DR, Weatherall DJ, Clegg JB. Relative roles of genetic factors, dietary deficiency, and infection in anaemia in Vanuatu, South West Pacific. *Lancet* 1985;**ii**:1025–8.
37 Stevens DW, Wainscoat JS, Ketley N, Timms P, Ayoub D, Shah R. The pathogenesis of hypochromic anaemia in Saudi infants. *J Trop Pediatr* 1989;**35**:301–5.
38 Miller V, Swaney S, Deinard A. Impact of the WIC program on the iron status of infants. *Pediatrics* 1985;**75**:100–5.
39 James J, Lawson P, Male P, Oakhill A. Preventing iron deficiency in preschool children by implementing an educational and screening programme in an inner city practice. *BMJ* 1989;**299**:838–40.

Archives of Disease in Childhood 1991; 66: 890–893

Accidents to children: the doctor's role. Education or environmental change?

J R Sibert

Department of Child Health, University of Wales College of Medicine, Llandough Hospital, Penarth, South Glamorgan CF6 1XX

Correspondence to: Dr Sibert.

Accidents are the most common cause of death in children in Britain. Six hundred and eighty eight children died in England and Wales in 1987.[1] They also cause significant handicap and suffering to children. Less serious accidents are very common in childhood with one fifth of the child population attending the accident and emergency department in a year.[2] The prevention of accidents to children is therefore being increasingly recognised as an important public health problem.[3] Doctors who treat children and see the effects of their accidents are in a unique position in society not only to diagnose child abuse but also to alert the community of the problem of childhood accidents and to take action to prevent accidents. What is more difficult is how this is to be achieved.

Education or environment?

It is very tempting to think that all is needed is to alert the public to the dangers of accidents to children by education campaigns. The evidence that these are effective is unconvincing. A programme directed at the parents of children to prevent home accidents (the Rockland County study) made no difference in accident rates between control and target families.[4] There was little evidence that the 'play it safe television programmes' made any impact on accident rates in children.[5] An education campaign with posters and literature in Cardiff only sensitised the population to trivial accidents.[6] Education campaigns may be ineffective because psychosocial stress is involved in the aetiology of many childhood accidents and parents are unlikely to remember safety propaganda at these times. Stress has been found to be related to road traffic accidents,[7] accidental childhood poisoning in children,[8] and to accidents as a whole.[9]

It is also tempting to look on accidents to children as a whole and think of general solutions to the problem. All the evidence points to the fact that accidents to children have been prevented by looking at an individual type of accident, looking at the detailed epidemiology of that accident, and evaluating a solution before its widespread introduction. In almost all the cases where accident prevention solutions have been shown to be effective those solutions have been ones that involve environmental change. Examples of environmental solutions that have been successful in preventing accidents to children include flame proofing nightdresses, fencing private swimming pools, car safety seats, smoke alarms, and child resistant containers in preventing accidental child poisoning.

Preventing accidental child poisoning

Accidental child poisoning is also an example where a single accident problem has been looked at in a methodological way and has been prevented by an environmental solution. The epidemiology has been studied and it has been found that pyschosocial stress is important in its aetiology.[8] [10] Education campaigns have been evaluated and found to be ineffective.[11] [12] The environmental solution of child resistant containers was first suggested in 1959 by Dr Jay Arena in Durham, North Carolina.[13] These containers were evaluated in a community in the United States by Scherz where poisoning cases were reduced from 147 to 17 cases per year by the use of child resistant closures. After this success they were introduced for aspirin preparations and reduced poisoning episodes by approximately 50% in the United States[15] and 75% in Britain.[16]

What can doctors and other health care professionals do?

Although education campaigns may not be effective there is much that can be done to prevent accidents to children. In a study in Newcastle, Colver and his colleagues found that health visitors visiting the home giving specific attention to accident prevention can make differences in the way that families behave, in particular with regard to the installation of safety equipment.[17] The introduction of a child surveillance programme by general practitioners and health visitors[18] provides an ideal opportunity to make the home and the child's surroundings safer by environmental change.

Doctors see the effects of accidents and have a unique role in influencing the community on child safety. They cannot act alone in accident prevention and many other professionals such as architects, traffic engineers, and fire safety officers need to be involved as well as health professionals. On a national basis the Child Accident Prevention Trust has brought these disciplines together. Locally child accident committees have been shown to be effective in preventing accidents by a coordinated multidisciplinary approach.[19] Doctors, in particular the consultant paediatrician (community child health), should play their part in the formation of these committees.

Solutions for preventing individual accidents to children

PEDESTRIAN ROAD TRAFFIC ACCIDENTS

Road traffic accidents remain a major challenge in accident prevention in childhood. Boys between 5 and 8 years are at maximum risk. Children under the age of 8 years are not able to estimate the speed or dangers of traffic,[20] nor to foresee dangerous situations,[21] and parents may overestimate the ability of their children to handle traffic and let them go out on the road unsupervised. Sharples and her colleagues looked at deaths from head injury in the Northern region and found that 72% of these deaths occurred between 3 pm and 9 pm and mostly to boys playing after school.[22]

Safety and traffic education are therefore not likely to prevent road traffic accidents by themselves. Pease and Preston found that kerb drill was not perceived by young children to detect traffic and was thought sufficient by itself to ward off the dangers of the road.[23] Firth found that 'adequate explanations of exactly what is involved in road safety given by very few children'.[24] In Britain it has been suggested that the Green Cross Code prevented accidents when it was introduced but careful analysis of the figures suggests this was not the case.[25]

The most important means of preventing these pedestrian road traffic accidents is by modification of the environment. This can be done by redesigning residential areas to give priority to pedestrians and to separate them from traffic. The speed of traffic can be reduced by speed bumps and safe crossings can be provided. Sensitive schemes such as the 'Woonerf',[26] an area in which the residential function clearly predominates over any provisions for traffic in the Netherlands, are good examples of what can be done. The provision of play areas and generally improving the environment will reduce the number of children on dangerous streets.

ACCIDENTS TO CHILD PASSENGERS IN CARS

There is good evidence that seat belts are effective in preventing death and serious injury and since 1983, when legislation was introduced compelling the wearing of seat belts in front seats of vehicles, serious injuries have fallen as much as 20%. There is good evidence also that child restraint systems also prevent injury and death. The Transport and Road Research Laboratory found that no child died in a two year period when in a restraint whereas 264 non-restrained children were killed in that time.[27] Scherz found in Washington State USA that serious injuries were much less common in restrained children than non-restrained children.[28] Encouraging parents to obey the law and carry children in cars in approved restraints should form part of a child surveillance programme. The concept first ride-safe ride is much to be encouraged.

BICYCLE ACCIDENTS

There are factors in bicycle design that are important to safety. For example the high rise bicycle that was introduced into Britain in the late 1960s and early 1970s, had features such as the centre of gravity behind the back wheel when the rider was mounted that made it more dangerous than standard models.[29] Improvements in design have now meant that this model has been superseded. Parents should be encouraged to give thought to the type of bicycle that they buy for their child and to the proper maintenance of chain, gear, and brakes. Bicycle training for children also seems sensible.

The majority of the severe injuries that children have are those to the head and a boy has a one in 80 chance of having a bicycle head injury severe enough for admission to hospital in his childhood.[30] Cycle helmets are a logical solution to this problem. At present, this type of protection is not easily available and is expensive. A first step in their more widespread use would be to ensure that they are cheap and easy to buy. This is being encouraged in some areas at present.[31] A new British standard is now available.

BURNS AND SCALDS

The problem of nightdress fires causing horrific burns to girls was a major problem in the immediate postwar years. The environmental solution of fire retardant nightwear and probably also the reduction of open fires has reduced this problem to a small one.

On the other hand the majority of deaths from burns in children are due to house fires and these house fires remain a major problem with nearly 100 children dying in England and Wales in a year.[1] These house fires are particularly common in poorer families and many of them are due to the inflammability of upholstered foam furniture. The change to fire retardant foam early in 1988 is much to be welcomed as a clearly advantageous environmental measure but it will take some time for all the dangerous furniture to be out of homes.

Education campaigns have been shown to be ineffective in influencing behaviour regarding fire safety.[32] Smoke alarms have been shown to be effective in reducing problems from house fires[33] and now should be in every home. Encouraging families with children to have smoke alarms fitted should be an important part of a child surveillance programme.

Within the home many children scald themselves from kettles. The use of curled flexes to prevent flexes hanging over work surfaces so that they can easily be pulled by children is a simple environmental measure that can prevent some scald accidents to children. Similarly many children scald themselves from pulling on saucepan handles overhanging on cookers. This can be prevented by cooker guards or by placing other kitchen units beside cookers.

DROWNING

Drowning remains a significant problem in childhood with approximately 50 children dying each year in England and Wales.[1] Research has suggested that supervision within public pools has reduced deaths in a significant number and in 1988 no children died in a public pool in Britain.[34] On the other hand drowning in private pools and garden ponds remains a major problem. Research in Australia by Pearn and Nixon has suggested that drowning is 10 times more common in cities without fencing to private pools by regulation than those that have regulations with fencing.[35] Drowning in the bath in very young children remains a problem. A child surveillance programme should include making certain that garden ponds are fenced, drained, or have a metal mesh under the surface, make certain that garden swimming pools are fenced, and emphasise the dangers of leaving young children in a bath unattended.

PLAYGROUND INJURIES

The challenge of playground accidents was highlighted by Illingworth *et al.*[36] There are clear design issues which are important.[37] Surfaces should be impact absorbing such as bark or special rubber tiles and not be hard like concrete. Slides should go down natural slopes and not have ladders to climb. Roundabouts should not be designed so children's feet can be trapped underneath. Swings should have impact absorbing seats and be fenced to prevent children running across them. Climbing frames should be built to encourage horizontal not vertical play.

GLASS ACCIDENTS

The problem of glass accidents was highlighted by Jackson,[38] and significant numbers of children are injured from falling through glass. This may result in haemorrhage and nerve damage. These injuries can be prevented by the use of safety glass, which is laminated, or by fitting a safety film on existing glass to make it less likely to shatter on impact. Safety glass has now to be used in doors in new houses because of building regulations. Advising on glass within the home should be part of a child surveillance programme.

FALLS

Falls are also the commonest cause of presentation to the accident and emergency department[2] and cause a significant number of deaths in childhood.[39] They have a varied aetiology.

Falls can be from one level to another. Children may be dropped, fall from furniture, fall down the stairs, fall from toys, and fall from windows. Falls downstairs are a particular problem for toddlers. Much can be done to prevent them by better stair design. Stair gates are valuable, especially for the busy mother in poorly designed properties. Their use can be encouraged by the health visitor and should be part of a child surveillance programme. Open stairs with wide gaps between balustrades may be fine aesthetically but dangerous for young children. In 1985 building regulations were changed to make certain that a 100 mm sphere could not be passed through any opening or guarding to a flight of stairs.

The danger of falls from baby walkers has been highlighted and they can no longer be advised for children's use.[40] Poor window catches and design cause a number of accidents, particularly in high rise flats. The introduction of safe catches or window guards will reduce these accidents. Indeed, in New York City a programme providing free window guards ('the children can't fly program'), has been successful in preventing window falls in a poor area of New York.[41]

Checklist for doctors and health visitors to prevent accidents as part of a programme of child surveillance

- Discover particular accident problems in the district
- Establish links with councillors, parents, organisations, etc
- Deal with each accident individually.

TO PREVENT ROAD TRAFFIC ACCIDENTS

- Encourage parents of children 8 years old or less to take them to school
- Encourage use of play areas for children
- Encourage local action in dealing with dangerous road situations—particularly near schools
- Encourage use of car safety seats for children. Try and make 'first ride-safe ride'
- Encourage the use of bicycle safety helmets
- Encourage parents to let their children attend bicycle riding instruction and to maintain the bicycles adequately.

TO PREVENT BURNS AND SCALDS

- Encourage disposal of dangerous foam furniture
- Encourage use of smoke alarms
- Discourage open fires. If they have to be used use fireguards
- Emphasise dangers of hot liquids
- Place kitchen units on either side of cooker or fit cooker guard
- Use coiled flex electric kettles
- Encourage safe use of fireworks.

TO PREVENT DROWNING

- Fence private pools. Take care with pool cover design. Drain pools in winter
- Supervise swimming adequately especially to non-municipal public pools, lakes, and rivers
- Teach children to swim
- Advise parents regarding dangers of young children in baths and in garden ponds
- Fence, grid, or remove garden ponds
- Use life jackets and buoyancy aids for children in boats.

TO PREVENT RECREATIONAL ACCIDENTS

- Find playgrounds in the district and check on design and surfaces. Investigate any playground injuries

- Influence safe design with local councils
- Be aware of dangers of dogs (as part of health visitor's accident prevention package)
- Keep dogs out of playgrounds
- Supervise sporting activities in children
- Encourage use of head protection for horse riding as British standard (BS 6473).

TO PREVENT 'ARCHITECTURAL' ACCIDENTS AND FALLS
- Check design of stairs for child safety
- Advise stair gates to families with toddlers in house
- Advise against baby walkers
- Check window and balcony design for child safety. Advise catches if necessary
- Advise safety glass or safety film for low level glazing.

TO PREVENT ACCIDENTAL POISONING
- Encourage use of child resistant containers by pharmacists
- Encourage storage of medicines and household products away from children
- Discourage prescribing of quinine and barbiturates, etc.

1 Office of Population Censuses and Surveys. *Deaths by accidents and violence*. London: OPCS, 1988. (Quarterly Monitors DH4 Series.)
2 Sibert JR, Maddocks GB, Brown M. Childhood accidents—an endemic of epidemic proportions. *Arch Dis Child* 1981; **56**:225–7.
3 Child Accident Prevention Trust. *Basic principles of child accident prevention*. London: CAPT, 1989.
4 Schlesinger ER, Dickson DG, Westaby J, Logrillo VM, Maiwald AA. A controlled study of health education in accident prevention: the Rockland County child injury project. *Am J Dis Child* 1966;**111**:490–6.
5 Sibert JR, Williams H. Medicine and the media. *BMJ* 1983; **286**:1893.
6 Minchom P, Sibert JR. Does health education prevent childhood accidents. *Postgrad Med J* 1984;**60**:260–2.
7 Backett EM, Johnston AM. Social pattern of road accidents to childhood. Some characteristics of vunerable families. *BMJ* 1959;**i**:403–9.
8 Sibert JR. Stress in families of children who have ingested poisons. *BMJ* 1975;**ii**:87–9.
9 Brown GW, Davidson S. Social class, psychiatric disorder of mother and accidents to children. *Lancet* 1978;**i**:378–81.
10 Bithoney WG, Snyder J, Michalek J, Newberger EH. Childhood ingestations as symptoms of family distress. *Am J Dis Child* 1986;**139**:456–9.
11 Harris DW, Karindiker DS, Spencer MG, Leach RH, Bower AC, Mander GA. Returned medicines campaign in Birmingham 1977. *Lancet* 1979;**ii**:599.
12 Ferguson DM, Horwood LJ, Beautrais MA, Shannon FT. A controlled trial of a poison prevention method. *Pediatrics* 1982;**69**:515.
13 Arena JM. Safety closure caps. JAMA 1959;**169**:1187–8.
14 Scherz RG. Prevention of childhood poisoning. *Pediatr Clin North Am* 1970;**17**:713.
15 Clarke A, Walton WW. Effect of safety packaging on aspirin ingestion by children. *Pediatrics* 1979;**63**:687–93.
16 Sibert JR, Craft AW, Jackson RH. Child resistant packaging and accidental child poisoning. *Lancet* 1977;**ii**:289–90.
17 Colver AF, Hutchinson PJ, Judson EC. Promoting children's home safety. *BMJ* 1982;**285**:1177–80.
18 Hall DMB, ed. *Health for all children*. Oxford: Oxford University Press, 1989.
19 Schelp L. Community intervention and changes in accident pattern in a rural Swedish municipality. *Health Promotion* 1979;**2**:109–25.
20 Howarth CI, Routledge DA, Repetto-Wright R. An analysis of road accidents involving child pedestrians. *Ergonomics* 1974;**17**:319–30.
21 Kohler L, Ljungblom B-A. *Child development and traffic behaviour. Traffic and children's health*. Stockholm: Nordic School of Public Health, 1987.
22 Sharples PM, Storey A, Anysley Green A, Eyre JA. Avoidable factors contributing to death of children with head injury. *BMJ* 1990;**300**:87–91.
23 Pease K, Preston B. Road safety education for young children. *Br J Educ Psychol* 1967;**37**:305–13.
24 Firth DE. *Roads and road saftey—descriptions given by 400 children*. Crowthorne, Berkshire: Transport and Road Research Laboratory, 1975. (TRRL Supplementary Report 138UC.)
25 Grayson GB. The identification of training objectives: what shall we tell the children? *Accid Anal Prev* 1981;**13**:169–73.
26 Royal Dutch Touring Club. *Woonerf*. The Hague, Netherlands: Royal Dutch Touring Club, 1977. (Available from: the Royal Dutch Touring Club, PO Box 93200, The Hague, Netherlands.)
27 Transport and Road Research Laboratory. *The protection of children in cars*. Crowthorne, Berkshire: TRRL, 1974. (Leaflet 345.)
28 Scherz RG. Restraint systems for the prevention of injury to children in automobile accidents. *Am J Public Health* 1976; **66**:451.
29 Sibert JR, Newcombe RG. Bicycle injuries in childhood. *BMJ* 1977;**i**:613–4.
30 Clarke AJ, Sibert JR. Why child cyclists should wear helmets. *Practitioner* 1986;**230**:513–4.
31 Walker A. Cycling in cities. *BMJ* 1990;**301**:80.
32 McCabe M, Moore H. Is national fire safety week a waste of time? *Fire Prevention* 1990;**232**:12–4.
33 US Fire Administration. *An evaluation of residential smoke detectors under actual field conditions*. Final Report EMW-C-002. Washington DC: US Fire Administration, 1980.
34 Kemp A, Sibert JR. Drowning and near drowning in children. *Proceedings of the Annual Meeting of the British Paediatric Association*. Warwick, April 1990.
35 Pearn JH, Nixon J. Are swimming pools becoming more dangerous? *Med J Aust* 1977;**2**:702–4.
36 Illingworth CW, Brennan P, Jay A, Al-Rawif ER, Collier M. 200 injuries caused by playground equipment. *BMJ* 1975; **iv**:332–4.
37 National Playing Fields Association. *Playground management and safety*. London: NPFA, 1989.
38 Jackson RH. Lacerations from glass in childhood. *BMJ* 1981;**283**:1310–2.
39 Nixon J, Jackson H, Hayes M. *An analysis of childhood falls involving stairs and bannisters*. London: Consumer Safety Unit, Department of Trade and Industry, 1987.
40 Glendill DNS, Robson WV, Cudmore RE, Tavistock RR. Baby walkers—time to take a stand. *Arch Dis Child* 1987; **62**:491–4.
41 Speyel CM, Linderman F. Children can't fly. A program to prevent mobility and mortality from window falls. *Am J Public Health* 1977;**68**:1143–7.

Archives of Disease in Childhood 1991; **66:** 894–899

PERSONAL PAPER

Paediatric care in general practice

Stuart Carne

The Royal College of General Practitioners, 14 Princes Gate, Hyde Park, London SW7 1PU

Correspondence to:
Dr Carne, *president.*

I qualified in 1950 and, before I did my national service in the Royal Air Force, I was fortunate enough to get an additional year's experience as a rotating house officer at the Queen Elizabeth Hospital for Children in Hackney.

I was appointed medical officer to the RAF Medical Training Establishment where newly commissioned medical officers (like me, mainly national service) were taught how to be RAF officers and new airmen recruits were taught to be nursing orderlies. My main task was to take the early morning sick parade: 7.30 am on ordinary mornings; 6·30 am when the commanding officer had his parade.

Once a week I had to examine each new batch of recruits. They had all been examined at least twice previously: once before they were called up and then again when they arrived at the initial training centre at Padgate. Nevertheless, a few of them had quite severe disabilities—mainly orthopaedic or cardiac—and were clearly unfit for service duties.

As they were going to work as nursing orderlies, I also had to give them all a Mantoux test. Most were positive, to varying degrees. (The most violent reaction was in the son of a thoracic surgeon who, it transpired, had watched his father at work on many occasions.) Having already done two hospital ear, nose, and throat appointments (one adult, one paediatric) I had seen a lot of tonsillectomies—and even tried my hand at it, not very successfully! Cervical adenitis, much of it tuberculous, was not uncommon in those days and so, too, was tuberculous mesenteric adenitis. I wondered whether the Mantoux reaction was in any way related to a previous tonsillectomy or appendicectomy. A pilot study revealed no obvious connection but there did seem to be a connection between the frequency of these operations and the recruit's social class—though not between social class and the Mantoux reaction. Both operations were performed more frequently in recruits who came from a higher social background.

I therefore rewrote my protocol and decided to look at the incidence of tonsillectomy and appendicectomy. For good measure I added circumcision to my data. (As there was no national service for women, there were very few female nursing orderly recruits.) The RAF were extremely cooperative and provided me with statistical assistance. My hypothesis was confirmed and the editor of the *British Medical Journal* saw fit to publish my paper,[1] though he 'invited' me to change the title from 'Three popular operations' to 'The incidence of tonsillectomy, circumcision and appendicectomy among RAF recruits'.

My time in the RAF coincided with the evacuation by the British forces from the Suez Canal Zone. The wives and children were sent on ahead. Those without their own homes in the UK were housed in a camp outside Blackpool or lodged during the winter in boarding houses in the town. In addition to my duties as medical officer at the Medical Training Establishment, I was posted as medical officer to these families, presumably because of my paediatric interest and experience.

My experience with these families taught me a lot: dare I say, more than most of my previous hospital experience. The mothers were constantly seeking medical help for their problems, yet pathology as I had been taught it was scant. More often than not it was a child who was brought to me, not the mother; and very often the child or a sibling was brought back at fairly frequent intervals.

At first I thought that my clinical skills had failed me, probably because I was usually dealing only with the presenting symptom—which is what we tended to do in those days in primary care. I therefore arranged to see the more persistent attenders at special sessions in order to give myself time to carry out a proper hospital type assessment. Instead of taking a superficial history of the more physical aspects of the problem, I probed extensively into the family history and its social aspects. I discovered two things: the presenting medical problem of the child was rarely the mother's major worry; and secondly, at the end of a consultation, many mothers thanked me 'for listening'. Later I read Michael Balint's seminal textbook: *The Doctor, His Patient and The Illness* and, for the first time, found in print an answer to the conundrum that we call general practice.[2]

My first proper job in general practice was in All Saints Road in North Kensington where I spent three years as an assistant. In 1957 I got an Executive Council vacancy in Shepherds Bush—about a mile south of the Royal Postgraduate Medical School at Hammersmith Hospital and half a mile east of Queen Charlotte's Hospital. The previous general practitioner (GP) in the practice was age 75+ and terminally ill. His wife—an ex-nurse—had been running the practice for the previous year or so! Records were scanty as were the equipment and facilities for clinical examination. Now that I had my own practice, I could organise it in the way I believed best to improve the quality of care. I had shelves put in a corridor to store records and purchased an examination couch. I also bought a typewriter and my wife became my (unpaid) secretary/receptionist. All hospital letters were typed so that they were at least legible. By keeping a copy of all my letters, I was able to compare the outcome with my thoughts when I referred the patient: a sort of audit.

For the first five years in Shepherds Bush I lived above the surgery. I introduced a well baby clinic, which was held once a week on Wednesday mornings. I announced the fact on the plate in my front garden. The local BMA secretary wrote me a stern warning about advertising and I had to remove the notice of my clinic!

I met the local London County Council divisional medical officer and she offered to send one of her health visitors to my weekly baby clinic. So began a 16 year relationship with the same health visitor. The time she spent in my practice steadily increased till she became full time. Indeed, as the practice expanded we found it necessary to have two health visitors attached full time. The practice itself has grown from the original list of 1400 which I took over in 1957 to 14 000 patients with seven GP partners, four of whom had been trainees in the practice. In 1967 we moved into the Grove Health Centre, which was only the second purpose built health centre in London. We are now in the process of planning a new building, about three times the size of the present one. Such is progress: though I believe that small can also be beautiful.

In the early years of undergraduate training in general practice, almost half the St Mary's Hospital Medical School students came to the Grove Health Centre. Among that group were two who are now consultants at Hammersmith Hospital: one is a neonatologist, the other a geriatrician (which must, surely, say something for the generality of general practice!).

For many years I was a GP trainer. Later I became the first course organiser at the Royal Postgraduate Medical School, with the title of 'Senior tutor in general practice'. (The only privilege which went with that appointment was parking rights in the front of the hospital!) The post of course organiser is now filled by one of my partners who, himself, had been the first GP trainee at Hammersmith Hospital. In fact, the practice now has such a heavy teaching commitment elsewhere, and space is so limited in the health centre, we can no longer have a trainee in the practice and have to look outside for the stimulus that postgraduate students bring to medical practice.

I have a special interest in paediatrics, whether it is dealing with the children when they are sick or dealing with children when they are well, such as at a child health clinic (which I still prefer to call a well baby clinic). Indeed, as I frequently tell the mothers (and now, also, the fathers): 'How can I look after your child properly when he is sick if I do not know what he is like when he is well?'

Until my presidential duties restricted my time, I ran the well baby clinic in the practice. We have three sessions a week devoted specifically to children under 5 years. The first is for routine child health surveillance and is run jointly by one or two of the GPs together with the health visitors. The second session is organised by the health visitors. Parents always have direct access to the health visitors whenever they are there (that is, office hours). Because we are in the same building, referral from doctor to health visitors—and vice versa—is uncomplicated.

Immunisations are done at a separate session. I am often asked why immunisations are not given at the child health surveillance or health visitors' sessions. Would it not save mothers' (and doctors') time? My answer is that health surveillance clinics should be conducted in a happy relaxed atmosphere. Mothers are coming to be reassured that their baby is normal and that they are doing a good job as mothers. (True disabilities are rare—as opposed to the number of *normal* children referred from clinics to a specialist, which reflects not a need for treatment of the baby but better education of the clinician conducting the clinic.) Immunisation sessions are often traumatic. Waiting mothers are anxious: 'Is it going to hurt my baby?'; and the baby, seeing other infants leaving the room crying, is also likely to be upset.

Nevertheless, if a baby attending a surveillance clinic is overdue an immunisation, we will offer it on the spot but—probably because of close health visitor and GP collaboration—attendance rates for immunisation are, by inner city standards, good.

Though I have a special interest in child health, I do not see all, or even the majority of sick children in the practice. I am not a GP paediatrician who—when we think about it—is neither GP nor paediatrician. Occasionally I am asked by a partner to comment on a child health problem but I am as likely to be asked my views on clinical problems not related to children. If and when we want another opinion, it is from a specialist that we want it (which is why we will sometimes complain that a child referred for a consultant opinion in outpatients is seen by a registrar or even a senior house officer).

Expertise is a combination of knowledge and experience. Knowledge we can all acquire, either by reading the literature or attending (didactic) lectures. We have to wait for experience to be available. In Britain there are, roughly speaking, 100 GPs for every paediatrician. A British paediatrician is therefore 100 times more likely to have had to deal with a rare problem than a GP. Similarly, for every paediatric specialist in the UK there are—proportionate to the population—almost 50 paediatricians in the United States, most of them delivering primary care paediatrics.

The British specialist paediatrician can thus justify his claim to expertise because far more of his time is devoted to the less common problems. Either we dilute his experience or we retain the present division between GP and specialist.

It is no loss of status in the eyes of my patients for me as a GP to seek a second opinion. Were I called a paediatrician, I would have to explain why I need another paediatrician to advise me. A GP referring a patient to a specialist is no different from one specialist referring to another specialist.

Thus I believe that the British system of having a generalist deliver primary care and leaving specialists to concentrate on secondary (and tertiary) care has much to commend it.

There are a number of diseases I almost certainly see more often than my hospital based colleagues—for example, upper respiratory tract infections and all the associated complications such as otitis media and tonsillectomy. (Yes, I do mean the complication of tonsillectomy, not the indications for that operation, which I believe to be very rare.)

The ritual sacrifice of parts of Waldeyer's ring has remained a special interest ever since my RAF study. What are the criteria for saying

[redacted]

to others, limbs or trunk covered with a seborrhoeic eruption are accepted as part of life. Also relevant may be the attitude of the doctor. The authoritarian physician who would expunge all pathology off the skin is likely to prescribe medication that is both more potent and more expensive, though this does not necessarily lead to an improved dermis.

Young children who have frequent spells of coughing, especially at night, are seen frequently both in hospital and general practice. Inquiries of other mothers reveal that there are even more children who cough frequently and are not brought to the doctor. Often asthma lies at the root cause but, in infants, treatment of the bronchospasm is not very satisfactory in eliminating the troublesome cough. I always ask the mother how much the child's night time cough worries *her* and how much it disturbs the baby.

I am deputising for Mollie Smith, the district nurse who cannot be here today'. 'I am Dr Bloggs: I am standing in for Dr Snooks, the paediatrician who is away at a conference this week'. Nor do I regard it as reasonable to expect a GP to attend a case conference at what is, for him, a particularly busy time in the practice, such as 10 am on a Monday morning.

Furthermore, I cannot automatically be bound by conference decisions. As a GP I have to make up my own mind. I am personally responsible, both within the NHS and in law, for all my actions. It is no defence for me to say: 'I acted on the advice of X, a specialist in that field'. (I was recently at a Department of Health meeting when a consultant paediatrician was surprised to learn that GPs do not have to comply with hospital recommended prescriptions unless they themselves are in agreement with the decision. The choice of medication is that of the paediatrician or the GP who actually writes the prescription: neither can order the other what to do.)

'Emergency' housecalls to children loom large in the traditions of general practice; many of my hospital colleagues always assume this to be a major part of my work. Parents do worry about their children, some more than others, and especially with their first child. The problem for many is aggravated by the absence not only of a nuclear family but also of an extended family. I suspect—though I cannot prove it—that close collaboration in my practice with the health visitors adds to the feeling of protection we can offer these mothers. I long ago realised that if good quality care is available 'in hours', the number of 'out of hours' calls falls considerably.[5]

We run an appointment system which is valued as much by working class mothers as it is by the 'yuppies' who now live in Shepherds Bush. It is resented by an equal proportion in both groups. But we also accept 'walk-in' consultations—without (I hope) the patient having to justify the request with a receptionist.

Occasionally there are unnecessary requests for emergency house calls. A common variety belongs to the 'dad's home from the pub syndrome'. Father comes home late for his supper, rather more inebriated than is good for him. 'Where is my meal?' he demands. 'There isn't any meal'. 'Why isn't there a meal?' he asks his wife, now herself becoming a bit defensive. 'Because the kid's been ill all day'. At this point husband and wife (or wife and 'partner') recognise an opportunity for reconciliation. 'Let's call the doctor'. On my arrival at the home, the healthiest person I see is often the child; but this is not the occasion for berating the parents for calling me out unnecessarily.

Having examined the child I say: 'Fortunately baby is not very ill. If you are still worried about him in the morning, why not bring him round to the surgery?' What I certainly do not do is offer them a sachet of an antibiotic or Calpol, for that action would convince them that medication was necessary and therefore they were right to have called me. (I always remember the teaching of the great Carlisle Potter on the subject of fractious babies: 'a large dose of sedative is the best remedy' he would say; 'no, not for the baby but for the mother!').

In my first weeks in general practice, I saw one child with tuberculous meningitis and another with pyloric stenosis. Since then I have seen only one other baby with pyloric stenosis: and that was about 25 years ago. I have not seen another case of tuberculous meningitis. I have seen three cases of meningitis and—by the grace of God—I diagnosed all three. In one, I recognised the high pitched cry—and had an argument over the phone with 'the duty paediatrician' about its significance. I hope that if, and when, I see my first child with epiglottitis I will remember not to try and examine the throat with a tongue depressor.

Appendicitis *seems* to be getting much rarer. I have not seen a case for over two years, though one of my younger partners sent a child to hospital with that diagnosis a few weeks ago.

We have always to remember that, in the NHS, if a GP does miss a diagnosis, sooner or later the hospital discharge summary—however the child got to hospital—will bring the error to light.

Acute attacks of asthma are distressing to the doctor as well as to the patient and the parents; they can also be life threatening. I am not in favour of the current vogue for nebulisers, which seem to me to be underused by some and abused by others. I believe that if nebulisation is necessary, a course of oral steroids is almost always also needed. The various 'spacer' devices which can be attached to an ordinary inhaler are, anyway, almost as effective as a nebuliser—and far less dramatic. My own preference (going back to my days at Queen Elizabeth Hospital almost 40 years ago) remains a short, sharp course of *oral* prednisolone, followed a few days later (when the child and the family are more relaxed) by better education on how they should manage the disease with ordinary inhalers. In most cases I find it quite safe to leave the family with a small supply of prednisolone for use in a future emergency. In my practice we do not issue repeat prescriptions without seeing the patients each time. We then issue enough medication to last until the next time it is *clinically* necessary to see the patient. Therefore it is easy to monitor the frequency and the quantity of steroids consumed and, hence, to recognise when to introduce inhaled steroids on a regular prophylactic basis.

From a general practice point of view diabetes in children is rare. The majority of us will have, at most, only one diabetic child on our list during the whole of our 30–35 years as a GP, and many will never have that responsibility. However, for 15 years I had the privilege of being medical officer to Palingswick House hostel for diabetic children, which was situated less than a mile from my surgery. At any one time there were 40–50 children with diabetes resident at the hostel, including some of the most difficult cases from all over the country. Before coming to Palingswick House, most of them had been absent from school for frequent and prolonged periods and in and out of hospitals. In most of the children the main problem was emotional: they and/or their family had not yet come to terms with the illness.[6] Without realising it was offering the service, what Palingswick House did was provide group therapy. The children supported each other. All of those who had not yet learned how to do it, including those of preschool age, were taught to administer their own insulin injections (but a nurse always checked the quantity loaded into the syringe). We taught them how to manage their own diabetes. In particular, we taught them how to reduce the frequency of 'hypo' attacks by understanding what was likely to bring one on and what preventive action to take. We relied on oral glucose or, in the early stages of an attack, any carbohydrate. It was rarely neces-

tory for infectious contaminating organisms (the result of which tests, anyway, will not be available in most cases until after the child has recovered).

In some cases, diarrhoea is attributed to a systemic infection, in particular of the respiratory tract (23% in the series of Conway *et al*[7]). Otitis media (generally classified with respiratory tract infections) is one of the most frequently blamed systemic infections for the cause of diarrhoea. The treatment is often an antibiotic. (Views differ as to the appropriateness of this treatment. Nevertheless, there are many doctors both in general and hospital practice who regard an antibiotic as the first line treatment of otitis

[redacted]

his house calls.[8] Stress can, therefore, often be detected in more subtle ways than it might be in a family seen for the first time.

Not infrequently, an acute emotional breakdown in the family will be presented as an apparently *medical* illness in one of the children. I have described elsewhere puerperal depression in the mother presenting as vomiting in the baby,[9] to which clinical picture I later gave the name of the 'Azazel syndrome' after the biblical story of the scapegoat who was sent into the wilderness of Azazel.[10] Equally, we always have to remember that, because there is emotional illness in a family, it does not mean that we can exclude a physical cause for the current presenting problem.

The care of children is a fundamental component of general practice. It is virtually impossible to do proper general practice—family medicine—without being involved in the treatment of sick children. It logically follows that if properly trained GPs are able to look after children when they are ill, they are also able to examine children when they are well. I therefore anticipate that the additional knowledge required for child health surveillance will be accepted as part of the core content of good general practice.

I have left to the last the issues that surround referral of children to hospital. Regrettably this is, all too often—especially in an inner city area—the only interface between GP and specialist.

The reasons why patients are referred for a specialist opinion are complex.[11] It is often assumed that the GP is passing a problem he cannot manage to a more senior member of the medical hierarchy, but that view is incorrect. Very often the specialist is being asked for his support in the management of a chronic condition for which there is no cure, such as catarrh or eczema. It is also to reassure the family that there is no need for active medical or surgical treatment, for example, most children with recurrent abdominal pain. If referral is to become rational and, hence, more cost effective it will be necessary for all three partners in the process—GP, specialist, and patient (or parents)—to understand the process more fully and its nuances.

We need to understand the difference between a 'consultation' and a 'referral'. A 'referral' is the handing over of the management of that illness by the GP to a specialist and his hospital based team. A 'consultation' implies the seeking of an opinion from a specialist with the intent that the ongoing management of the problem will be left in the hands of the GP. (The word 'consultation' is also used to describe what happens when a patient seeks the opinion of a doctor, whether it is GP or specialist.)

A 'second opinion' is, strictly speaking, not synonymous with either referral or consultation with a specialist. It was originally used to indicate the obtaining of another (and possibly different) opinion from a second specialist in the same field. If the term 'second opinion' is to be used to denote an ordinary referral or consultation, then it is important to remember that it is not possible to have a second opinion without having a 'first opinion', which should be provided by the general practitioner.

Early in my career I realised that, if I wanted to help sick children, I needed to know a lot more about their families. Furthermore, this was a field in which—to use the American expression—I felt comfortable. So I chose general practice, and I have never regretted it.

I would like to thank Professor Denis Pereira Gray and Dr Colin Waine for their helpful comments.

1 Carne S. Incidence of tonsillectomy, circumcision and appendicectomy among RAF recruits. *BMJ* 1956;**ii**:19–23.
2 Balint M. *The doctor, his patient and the illness.* London: Pitman Medical, 1957.
3 Mackie RM. *Clinical dermatology—an illustrated textbook.* Oxford: Oxford University Press, 1981:61.
4 Carne S. Some common skin disorders. In: Hart C, Bain J, eds. *Child care in general practice.* 3rd Ed. Edinburgh: Churchill Livingstone, 1989.
5 Working group of the Children's Committee. Out of hours social and health care. *Health Services Journal* 1980;**90** (suppl):759.
6 Carne S. Diabetes in children. *Proceedings of the Royal Society of Medicine* 1975;**68**:277–80.
7 Conway SP, Phillips PR, Panday S. Admission to hospital with gastroenteritis. *Arch Dis Child* 1990;**65**:579–84.
8 Pereira Gray DJ. Feeling at home. *J R Coll Gen Pract* 1978; **28**:6–17.
9 Carne S. The influence of the mother's health on her child. *Proceedings of the Royal Society of Medicine* 1966;**59**:1013–4.
10 Carne S. The Azazel syndrome: the child as scapegoat for a family illness. *Modern Medicine* 1989;**34**:595–6.
11 Carne S. A problem halved? *J R Coll Gen Pract* 1982;**32**: 10–31.

Archives of Disease in Childhood 1991; **66:** 900–903

PERSONAL PRACTICE

Use of movement analysis in understanding abnormalities of gait in cerebral palsy

J H Patrick

Orthotic Research and Locomotor Assessment Unit, (ORLAU), Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire SY10 7AG
J H Patrick

Correspondence to: Mr Patrick.

Orthopaedic surgeons and paediatricians rarely use gait laboratory studies to assist decision making in the treatment of walking diplegic patients with cerebral palsy. This is now changing because of a realisation that operations for cerebral palsy can be vastly improved using such analysis.

An unlikely stimulus came in spring 1990 from the media. BBC television showed a film about the progress of a spastic boy from south London who visited a movement analysis laboratory at Newington Children's Hospital, Connecticut, USA. There he was assessed using VICON kinematics, electromyography, and forceplate measurements. He then underwent surgery and physiotherapy. The results of the operations were not spectacular, but the technology and the touching pictures of a courageous boy with cerebral palsy were more important than 'results'.

Doctors and therapists have been stimulated to think of improvements in diagnostic methods and ways of achieving a better understanding of the biomechanics of walking in individual patients. A case is made here for reconsidering the place of surgery for many patients with cerebral palsy by undertaking bony procedures and release or lengthening of tendons after gait analysis has been carried out, on more mature children aged from 7–8 years.

Although the television commentary did not mention the source of the equipment, that used in this patient's analysis was British; such systems are no longer just research tools, as is shown by the work of our laboratory. Accurate three dimensional data about limb movements in space can be obtained and viewed at leisure by rerunning video film after conventional examination of the patient has identified some of the problems in the lower limbs. Such equipment, together with synchronous electromyographic recordings of muscle activity and kinetic force estimations in the lower limb, can now be used to measure each ambulatory spastic child. Movement analysis is now more than an interesting research tool, because it permits accurate diagnosis of the causes and effects of deformity in cerebral palsy. Consequently, treatment possibilities suggest themselves: physiotherapy, orthoses, or operation.

Traditional treatment regimen

For spastic children traditional methods of treatment have all included an assessment of walking potential. This is now a fine art, done best by skilled physiotherapists during a session of play, observation, and exercise usually undertaken during the first two years of life. In some areas of the country physiotherapists then remain at the forefront of physical management policy for that child. Orthopaedic surgeons and paediatricians usually accept this, as the attainment of walking is usually the province of physiotherapists and parents. Occasionally orthopaedic surgeons are asked to lengthen a tendon or muscle (usually at the groin or ankle), but the child grows and learns without much medical advice. Most children whose disability is confined to the legs, do walk; the more severely affected require wheelchairs, but there is a group for whom walking becomes increasingly difficult because of high energy costs of particular deformities which deleteriously affect walking.

Until recently we have been unable to analyse why some children apparently do well after operations, for example lengthening of the heel cord. Others, seemingly identical, adopt a

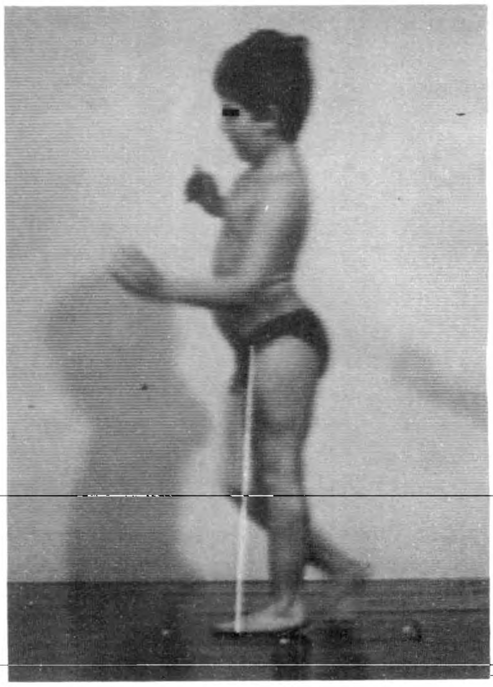


Figure 1 Left mid-stance phase in ORLAU movement analysis laboratory. Ground reaction vector line (representing body weight passing through force platform) shown as an extending moment to the left knee. Note slight equinus and lumbar lordosis caused by increased gastrocnemius and psoas muscle tone. (Figure is a polaroid photograph taken from a moving video film.)

crouch position after such operations. Why? Movement analysis now provides the answer (fig 1). A single frame photograph shows the body weight vector as a 'white line', accurately giving the position and direction of the body weight force as it is being applied to a Kistler force platform. Clearly, in this case, if the child has the heel cord lengthened then the ground reaction force vector may come to lie behind the knee (as in fig 2) unless the quadriceps can provide an opposing moment to straighten the knee. Often patients with cerebral palsy have quadriceps that are so weak that a 'crouch' is the only result of heel cord lengthening. This poor result (for some children) can now reliably be predicted, so the benefits of the analysis are explicit.

Current problems

Many children have heel cord operations that produce this 'crouch' position, because kinetic examinations such as ours are not generally available. The flexed knee and hip posture persists in spite of intense postoperative physiotherapy. Often surgical release of the flexion contracture of the knee is the next stage, and this has been called the 'birthday syndrome' because the child then undergoes still more physiotherapy, perhaps for another 6–12 months, until the surgeon releases the flexed hips of the 'crouch'.[1] This last operation may destroy the flexor power of the limb (which is necessary to initiate the swing phase of gait) if the psoas tendon and muscle retract into the pelvis, their insertion into the femur having been lost. Surgical intervention is therefore not always a success and some patients are made cosmetically worse. Surgical treatment is unfairly brought into disrepute if the biomechanics of that child are not known. Furthermore, neuromotor control is constantly maturing, and surgical intervention can be mistimed in growing children leading to bizarre gait problems in already handicapped spastic patients.

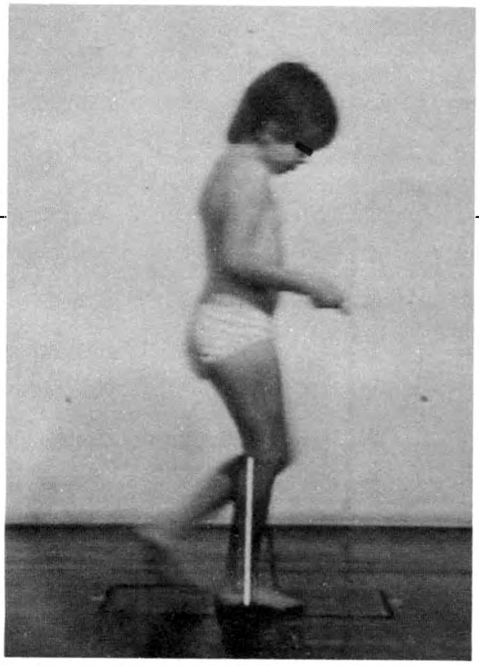


Figure 2 Right mid-stance on the force platform in ORLAU movement analysis laboratory. This girl has had her achilles tendon lengthened. The flexing moment to the knee is compensated for by quadriceps contraction—if this muscle weakens further she will 'crouch' by flexing hip and knee. (Figure is a polaroid photograph taken from a moving video film.)

OTHER PROBLEMS IN MANAGEMENT OF DIPLEGIC CHILDREN

Sutherland and Hagys[2] and Beals[3] have pointed out that all diplegic children with cerebral palsy who can walk, mature at a slow but definite rate, following the developmental pattern of neuromuscular control in their normal peers, but less efficiently. By the age of 7 years both groups have matured maximally, so surgeons should if possible wait until the plateau of maximum control has been reached before operating. We propose that no operation should be undertaken until movement analysis has been made at the age of about 7–8 years. If a disabling dynamic deformity is present earlier than this, then it is probably the result of increased tone in the lower limbs. Oppenheim has shown that in some patients selective rhizotomy may be helpful, although experience of this is still limited.[4]

Optimum management

If clinical maturation levels off during the seventh year it should be easy to analyse which mechnical faults are present in an individual child. Sensible treatment is then possible. The gait analysis, preceded by traditional history taking and static examination, is followed by kinematic analysis to show how the child walks. We can note in slow motion the action and duration of the stance and swing phases, we can see objectively the limitations of movement in individual joints, and we can compare these with normal gait performance. Electromyographic examination may be helpful as cooperation is quite possible in this age group. Energy studies to assess the work being done have important prognostic value, as high values will suggest eventual limitation of activity and the necessity for confinement to a wheelchair.

ANALYSIS OF LIMBS SEGMENTS

In many diplegic children with cerebral palsy the hip flexors, hamstrings and rectus femoris muscles (at the front of the knee) are too tight; the Achilles tendon has increased tone, and the adductor musculature contributes to excessive internal rotation at the hip. The classic 'diplegic walk' is the result: the child moves on tiptoe with the knees permanently bent to about 40°, with relative fixity of knee and hip motion during the swing phase.

Knees

Gage *et al* have shown that stiff knees are often caused by inappropriate contraction of the rectus femoris muscle; dynamic electromyographs can be made in the gait laboratory to show this. If confirmed, release or transfer of the rectus muscle tendon just above the knee is suggested. Knee motion during the swing phase is restored and elaborate, energy wasting swinging of the limb from the hip (circumduction) is eliminated.

Hips

The internal rotation of the femur at the hips is conventionally said to be the result of adductor overactivity, but kinematic and electromyographic analysis has shown that often iliopsoas or gracilis tightness are responsible. It is salutary to speculate how many adductor releases and rotatory femoral osteotomies have been done without simultaneous muscle balancing procedures, or because of lack of understanding of the cause of the internal rotation. Kinematic study can show internal rotation occurring after initial foot contact under the influence of gracilis and medial hamstring overactivity. An electromyographic analysis will confirm the point and permit accurate diagnosis, with a distinction being made between this type of internal rotation and the adduction/internal rotation of true adductor muscle spasticity.

A component of the 'crouch gait' is a dyna-

pitch of an ankle foot orthosis (below knee splint) can dramatically change the walk of a diplegic child. If the body weight vector is made to pass anterior to the knee, the weak quadriceps are strengthened. If the pitch is wrong, the ankle foot orthosis 'doesn't work', and the knee flexes more. This is confusing for child, parent, and orthotist. If the body weight forces are correctly distributed, walking is successful. These kinetic examinations can fine tune the ankle foot orthosis.

Energy expenditure

Surgery has been useful to many children with cerebral palsy, but measurement of the results has been inadequate. McGregor has shown that estimating changes in heart rate during walking and relating them to walking speed provides a simple, non-invasive and accurate method of evaluating treatment[7,8] This has been confirmed by Rose *et al.*[9] An index of the physiological cost (PCI) is derived in the laboratory during five timed walks on the gait track. The resting heart rate is subtracted from the exercising heart rate and divided by the speed. In our orginal group of nine patients with cerebral palsy who underwent movement analysis and

[redacted]

1 Rang M, Silver R, de la Garza J. Cerebral palsy. In: Lovell WW, Winter RB, eds. *Pediatric orthopedics*. Vol 1. 2nd Ed. Philadephia: Lippincott, 1986:345–96.

2 Sutherland DH, Hagys JL. Measurement of gait movements from motion picture film. *J Bone Joint Surg* 1990;**54A:** 787–97.

3 Beals RK. Spastic paraplegia and diplegia: an evaluation of non-surgical and surgical factors influencing the prognosis for ambulation. *J Bone Joint Surg* 1966;**48A:**827–46.

4 Oppenheim WL. Selective posterior rhizotomy for spastic cerebral palsy. *Clin Orthop* 1990;**253:**20–9.

5 Gage JR, Perry J, Hicks R, Koop S, Werntz JR. Rectus femoris transfer to improve knee function of children with cerebral palsy. *Dev Med Child Neurol* 1987;**29:**159–66.

6 Gage JR. Gait analysis for decision making in cerebral palsy. *Bulletin Hosp Jt Dis Orthop Inst* 1983;**43:**147–63.

7 MacGregor J. The objective measurement of physical performance with long term ambulatory physiological surveillance equipment (LAPSE). In: Stott FD, Raftery EB, Goulding L, eds. *Proceedings of 3rd International Symposium on Ambulatory Monitoring*. London: Academic Press 1979:29–39.

8 MacGregor J. The evaluation of patient performance using long-term ambulatory monitoring technique in the domiciliary environment. *Physiotherapy* 1981;**67:**30–3.

9 Rose J, Gamble JG, Burgos A, Medeiros J, Haskell WL. Energy expenditure index of walking for normal children and for children with cerebral palsy. *Dev Med Child Neurol* 1990;**32:**333–40.

Commentary

Gait laboratory analysis is a welcome attempt to introduce some science into a difficult and highly specialised area. Much orthopaedic energy has been directed to improve walking in children with spastic diplegia or hemiplegia. Even in the most experienced hands the results of surgery after careful *clinical* assessment are sometimes unpredictable and undesired.

Some reasons are not far to find. For example, intoeing is usually due to over activity of the medial hamstrings—and is corrected by lateral transfer of the semitendinosus. However, the psoas or other hip internal rotator may be responsible. The distinction can be made by analysis of the electromyogram during the walking cycle. Similarly analysis of the function of muscles which cross two joints such as the rectus femoris can assist operative decisions.[1] Normally the rectus is active in early swing to help hip flexion as well as to prevent excessive knee flexion. If the rectus is active in stance also, and the problem is excessive hip flexion in standing, proximal release is logical. If, however, there is activity after early swing and the problem is excessive extension leading to a stiff gait distal release or transfer is a better option.

It is still an article of faith that better planned surgery will yield better results. This is entirely reasonable as, unlike dystonia, weak muscles in *spastic* disorders remain weak after surgery. Over active muscles remain strong.

Great caution must be exercised, therefore, in extending this analysis to children with extrapyramidal involvement. Comparison of results of procedures based on gait analysis with results of clinically based procedures will not be easy but will be necessary to convince sceptics, and this includes funding authorities.

As with all such surgery, the role of a physiotherapist throughout is crucial.

The picture of practice that has emerged in the United States where several gait laboratories have developed considerable experience is for recommendations to be made to the referring clinician. It is for those who know the child and family best to decide with them whether in this particular child in his particular social and educational setting, this particular procedure will be appropriate. Clinical judgments have not been replaced by gait analysis. Instead, I hope they will become directed to more logically relevant questions.

R O ROBINSON
Newcomen Centre,
Guy's Hospital,
St Thomas Street,
London SE1 9RT

1 Perry J. Distal rectus femoris transfer. *Dev Med Child Neurol* 1987;27:153–8.

SISTER JOURNALS—UNITED STATES

American Journal of Diseases of Children
Robert Boyd had, to my mind, an easier reviewing task a few months ago as with no knowledge of Cyrillic script most of *Pediatriia* was incomprehensible to him. My smattering of Cyrillic is not required to review the *American Journal of Diseases of Children* (September 1990), so I am left deciding whether I am expected to comment on the journal or the individual articles therein: the wood or the trees?

Perhaps I should 'come clean' and admit that I am greatly influenced by the superficial appearance of things. I buy gramophone records for the attraction of the sleeves as much as for the quality of the recordings. For appearance this journal does not score highly. Despite being a publication of the American Medical Association, it lacks the artistic outside covers of its sister journal, the *Journal of the American Medical Association.* Inside it has similar problems. The relative merits of journal format can trigger involved arguments in editorial board meetings. Should a journal move to A4 size? Should there be one or two columns of print per page? These items are thought important in the battles to attract readers. *The American Journal of Diseases of Children* has three columns of very small print with about six words a line. Reading is tiresome as roughly every fourth line ends in a hyphenated word. The print is densely packed on the page with little break for illustrations or diagrams. The tables, on blue backgrounds surrounded by hard black lines, seem neither particularly easy to read nor attractive.*

But what of the science? The range of articles is wide and the topics covered significant: management of cardiovascular disease risk factors by primary care physicians; treatment of type 2a hyperlipidaemia in childhood (diet and fibre supplement); social and medical problems in children of heroin addicted parents (the problems you might expect with 37% unemployment, 16% prostitution, and 19% imprisonment among the parents). There are also articles on lawn dart injuries (read the journal to find out what a lawn dart is); an impressive update review of immunodeficiency diseases; assessment of growth hormone release by cycle exercise; ribovirin treatment guidelines; zinc metabolism in infant rhesus monkeys (with interesting addenda on compliance with the Animal Welfare Act and indicating approval by campus veterinarians—perhaps something we should stress more in Britain); a section on sports medicine; and bronchiolitis in south India. A jolly good read for the 'office paediatrician'.

Listing the articles tells us something about the journal. Among the 19 articles, three are from outside the USA: from Canada, Spain, and India. The USA is large and does not need other countries to provide material for her journals. Publication from abroad does, however, suggest an international readership rushing to publish, or waiting to read, the latest discoveries in the journal. The *American Journal of Diseases of Children* does not give the impression of having that kind of readership. Earth shattering discoveries are published elsewhere. Scanning the references listed in these 19 articles showed about 48 references to general paediatric journals, most of which were American publications. There were 10 references to the *Archives of Disease in Childhood,* yet only nine to the *American Journal of Diseases of Children* itself. Does this prove my point?

There is pleasure in self assessment with the 'case of the month' and the 'radiological case of the month'. Incorrect guesses with the latter can always be blamed on the difficulties of reproducing *x* rays in print! Letters and short items in overseas journals reveal particular national habits in an entertaining light. Is Nintendo incontinence a problem in your clinics? If so, have you tried recommending use of the 'pause' button on the video cassette recorder? Sometimes I feel very old and out of date!

E M E POSKITT

---

*The Americans must have felt as I did. In January 1991 the journal changed to a logo style title on the front cover and a predominantly two columns per page style internally.

LETTERS TO THE EDITOR

Recurrent abdominal pain of gastrointestinal disorder

SIR,—We were interested to read the study of van der Meer *et al*, which demonstrated a high incidence of duodenitis associated with abnormal intestinal permeability to ^{51}Cr-EDTA among children with recurrent abdominal pain.[1] We fully agree with their conclusion that duodenitis may play an important part in the pathogenesis of recurrent abdominal pain, although duodenitis rarely occurs without inflammation of other parts of the gastrointestinal tract.[2]

In a prospective study, duodenal, gastric, and oesophageal biopsies were obtained from 71 children with recurrent abdominal pain, aged 3 to 14 years (mean 8·6) who were undergoing upper gastrointestinal endoscopy for investigation of abdominal pain. We wanted to find out if there were gastroduodenal disorders (for example, duodenitis, gastritis, peptic ulcer) and if there was a relationship between these disorders and *Helicobacter pylori*. Patients were diagnosed as having recurrent abdominal pain if their symptoms fulfilled the criteria of Apley and Naish[3]: (i) at least three episodes of pain, (ii) if there was severe pain affecting the child's activities, (iii) if pain was occurring over a period of not less than three months, and (iv) if attacks continued in the year preceding the examination.

The duration of patients' symptoms before endoscopy ranged from 3–84 months (mean 16). The pain was periumbilical in 27 patients (38%), epigastric in 26 (37%), hypogastric in five (7%), diffuse in nine (13%), and had other locations in four patients: left upper quadrant (n=2), right upper quadrant (n=1), and right lower quadrant (n=1). The duration of attacks ranged from 1 to less than 5 minutes in eight patients (13%), from 5 to 60 minutes in 36 (51%), and from more than 60 minutes to all day in 27 (38%). The frequency of attacks was daily in 34 patients (48%), more than once a week in 21 (30%), once in every 2–4 weeks in seven (10%), and less than once a month in nine (13%). Forty children (56%) had the attacks of pain in the morning before getting up, 20 (28%) after breakfast, 34 (48%) after all other meals, 20 (28%) before all other meals, 18 (25%) at school, two (3%) immediately after sports, 12 (17%) in the afternoon, at home during play, and 18 (25%) at night, disrupting sleep.

Of these 71 children, 56 had suitable biopsy specimens from the duodenal bulb, 54 from the antrum, 55 from the body, 14 from the cardia, and 59 from the oesophagus. The histological findings in children studied are summarised in the table.

Histological findings in children studied

Histological findings	*No (%) of patients*
Normal duodenal mucosa	27 (48)
Mild duodenitis	29 (52)
Total	56
Normal antral mucosa	16 (30)
Superficial antral gastritis	38 (70)
Mild inflammation	24
Moderate inflammation	5
Active chronic gastritis	9
Total	54
Normal body mucosa	26 (47)
Superficial body gastritis	29 (53)
Mild inflammation	21
Moderate inflammation	3
Active chronic gastritis	5
Total	55
Superficial cardiac gastritis	14 (100)
Mild inflammation	14
Total	14
Normal oesophageal mucosa	32 (54)
Mild oesophagitis	27 (46)
Total	59

Sixty six of the children studied had an underlying gastroduodenal cause for their complaints: duodenitis (n=7), duodenitis and gastritis (n=13), gastritis (n=19, one of these children had gastric ulcer as well), duodenitis and oesophagitis (n=3), duodenitis plus gastritis and oesophagitis (n=6), gastritis and oesophagitis (n=14), and oesophagitis (n=4). *H pylori* colonisation was found in five of the 71 children studied, using both haematoxylin-eosin stained slides and cresyl fast violet staining.[4] Of these five patients, one had *H pylori* associated antral and body gastritis, and four *H pylori* antral gastritis only, although both antral and body gastritis were present in three of these four patients.

In the present study, though the presence of *H pylori* and antral gastritis is recognised, its association with recurrent abdominal pain is not established. These results provide further evidence that *H pylori* is not a primary pathogen of gastritis and support the hypothesis that *H pylori* may occasionally colonise gastric tissue as a result of inflammation rather than as a cause of it.

Our histological data show that duodenitis rarely occurs without inflammation of other parts of the gastrointestinal tract and that this condition is frequently associated with gastritis and less frequently with oesophagitis. These results, consistent with those of others,[2] raise the possibility that the same aetiological factors that cause gastritis may also be involved in the genesis of duodenitis.[2]

In a group of 51 children with non-specific abdominal pain, Oderda *et al* found oesophagitis in 11 cases, but the diagnosis was made endoscopically and not confirmed histologically.[5] Our data confirm that there is a high incidence of mild oesophagitis among the children studied and the diagnosis was made endoscopically and histologically. These data provide further evidence that there is a significant association of oesophagitis with gastritis or duodenitis. The significance of this association remains to be elucidated.

In conclusion, our data provide strong evidence that there is a gastrointestinal origin of these patients' complaints.

I MAVROMICHALIS
2nd Paediatric Department,
Aristotelian University of Thessaloniki,
AHEPA General Hospital,
Thessaloniki,
Greece

T H ZARAMBOUKAS
Department of Pathology,
Aristotelian University of Thessaloniki,
AHEPA General Hospital,
Thessaloniki,
Greece

P I RICHMAN
G SLAVIN
Department of Histopathology,
St Bartholomew's Hospital,
Medical College,
West Smithfield,
London

Presented in part at the Second Pan Pacific Congress of Paediatric Gastroenterology and Nutrition and First Oceanic Symposium on Paediatric Liver Transplantation in Cairns, Queensland, Australia, August 1990.

1 Van der Meer SB, Forgett PP, Arends JW. Abnormal small bowel permeability and duodenitis in recurrent abdominal pain. *Arch Dis Child* 1990;65:1311–9.
2 Beck IT. Duodenitis. In: Bockus HL, ed. *Gastroenterology*. Vol II. 4th Ed. Philadephia: Saunders, 1985:1403–21.
3 Apley J, Naish N. Recurrent abdominal pains: a field survey of 1000 school children. *Arch Dis Child* 1958;33:165–70.
4 Burnett RA, Brown IL, Findlay J. Cresyl fast violet staining method for campylobacter like organisms. *J Clin Pathol* 1987;40:353.
5 Oderda G, Vaira D, Holton J, Dowsett JF, Ansaldi N. Serum pepsinogen I and IgG antibody to Campylobacter pylori in non-specific abdominal pain in childhood. *Gut* 1989;30: 911–2.

When does slow weight gain become 'failure to thrive'?

SIR,—Edwards *et al* seek to derive, from the analysis of longitudinal growth data, a 'logical and generally accepted definition of failure to thrive' in order to 'enable vulnerable children to be identified at an early age'.[1] We contend that their diagnostic criteria are neither logical, nor are likely to gain general acceptance, for a number of reasons.

Firstly, the authors cite Smith *et al* as having demonstrated that the genetic contribution to a child's weight is 'greater by the age of 4 to 8 weeks' (than at birth, presumably). But Smith *et al* reported nothing of the sort. The paper cited does not even discuss weight gain but, as the title suggests, is concerned with shifting patterns of growth in length. A more relevant reference to the points being made is by Berkey *et al* who demonstrated that influences upon centile shifting in the first year of life include whether length or weight is being measured, the sex of the child, and whether the shift is towards or away from the 50th centile.[3] Edwards *et al* do not seem to distinguish between weight shifts upward and those shifts downward from the mean.

Diagnostic validity can be viewed as comprising face validity (that is, agreement by clinicians), descriptive validity (that is, a distinctive set of symptoms), and predictive validity (that is, a differentiation on one basis must predict differences in other areas). All they have really demonstrated is that infants whose weight persistently deviates (downwards) two or more major centiles from that position reached between four and eight weeks after birth will be rather smaller and lighter in the second year of life than those whose weight has not so deviated. Not a very surprising conclusion. Perhaps a corollary of this finding, a matter not entirely clear from the data presented, is that having deviated downwards in the first year by at least two major centiles an infant is unlikely to deviate up again in the second year. That would be more interesting but it is still not a validation of the concept of failure to thrive.

We would tend to agree with the recommendation of the Joint Working Party on Child Health Surveillance who 'were not convinced that the advantages conferred by regular weighing justify the resources required or the anxiety generated by inexpert interpretation of growth charts'.[4] It is essential to link the identification of a pattern of growth rmed 'failure to thrive' to some external iterion of developmental disadvantage, be iat 'psychosocial deprivation' or organic isease. Otherwise a time honoured preventive activity may become a source of unjustied parental concern.

B PORTER
D SKUSE
South London Growth and Development Study,
Institute of Child Health,
30 Guilford Street,
London WC1N 1EH

Edwards AGK, Halse PC, Parkin JM, Waterston AJR. Recognising failure to thrive in early childhood. *Arch Dis Child* 1990;**65**:1263–5.
Smith DW, Truog W, Rogers JE, *et al.* Shifting linear growth during infancy: illustration of genetic factors in growth from fetal life through infancy. *J Pediatr* 1976;**89**:225–30.
Berkey CS, Reed RB, Valadian I. Longitudinal growth standards for preschool children. *Ann Hum Biol* 1983;**10**:57–67.
Hall DMB, ed. *Health for all children: a programme for child health surveillance.* Report of the Joint Working Party on Child Health Surveillance. Oxford: Oxford University Press, 1989.

rs Edwards, Halse, and Waterston comment:
he three points made by Drs Porter and kuse cover the genetic influence on growth, ie diagnostic validity of persistent centile eviation, and the need for additional criteria r psychosocial disadvantage. Definitive iswers are not yet available on any of these oints. Smith's paper indeed discusses length ther than weight, but the key statement we xtracted from this work is that 'Those infants catching up" after birth usually do so in early fancy (0–3 months) whereas those "lagging own" tend to do so in mid-infancy (3–6 onths)'. We have provided the evidence in ır paper for the 4–8 week centile being a etter predictor of future growth than the rth centile.

Our findings show that babies whose weight eviates downwards according to our definion are distinctly different in the second year om babies whose weight does not deviate: ey are not only lighter, but also shorter and inner. We therefore believe that we have entified a different population of babies and iggest that these are children who may be garded as vulnerable and worthy of psychocial assessment. We believe that these findgs demonstrate the value of regular weighing children. Concerning the meaning of the rm 'failure to thrive', we agree with the *ancet* that this term, with its connotations emotional poverty, would be better andoned and replaced by 'failure to gain eight appropriately'.[1]

Previous definitions of failure to thrive hich relate to growth below the 3rd or 10th ntile do not take into account the growth ajectory, and are clearly unsatisfactory. We ink that ours is a considerable advance, if ill in need of further refinement.

Anonymous. Failure to thrive revisited. *Lancet* 1990;**336**:662–3.

aby Check score card

R,—The series of articles by A J Thornton, J Morley, and S J Green *et al* on the Baby heck score card make very interesting ading and represent a timely attempt to provide parents with a diagnostic tool to grade their infant's severity of illness.[1–4]

As a general practitioner I must admit to some reservations about many parents' capacity (particularly with first children) to document accurately their children's symptoms. I am frequently presented, as are my colleagues, with children whose parents cheerfully report that they have vomited everything they have been fed for the last 48 hours or longer, haven't passed urine for the last 24 hours, and are drowsy all the time ('He definitely isn't himself, doctor'!?). A set of symptoms belied by the fully hydrated and cheerful infant sitting in a wet nappy in the surgery ('He must have just done it').

This lack of reliability in parents' impressions of their children's symptoms is supported by a letter by Francy Pillo-Blocka *et al* from the Hospital of Sick Children in Toronto.[5] They reported on the subject of mothers of infants with gastro-oesophogeal reflux and their estimates of the quantity of fluid spilled on a baby's wash cloth. A spillage of 5 ml in volume produced a mean estimate of spillage of 35 ml (range 3–120 ml) and a 10 ml volume produced a mean estimate of spillage of 77 ml (range 7–240 ml). Of the 58 mothers tested, only one accurately assessed both volumes and the result was independent of education status or age of the mother. The authors advised caution in accepting parental impression of vomiting as a result.

I accept this finding only affects a small subsection of the Baby Check, but I would be very concerned about the widespread application of the score card before more work is done on the accuracy of parental assessment of individual signs and symptoms included in the score card.

D S SOWDEN
Measham Medical Unit,
Measham,
Burton-on-Trent DE12 7HR

1 Morley CJ, Thornton AJ, Cole TJ, Hewson PH, Fowler MA. Baby Check: a scoring system to grade the severity of acute systemic illness in babies under 6 months old. *Arch Dis Child* 1991;**66**:100–5.
2 Thornton AJ, Morley CJ, Green SJ, Cole TJ, Walker KA, Bonnett JM. Field trials of the Baby Check score card: mothers scoring their babies at home. *Arch Dis Child* 1991;**66**: 106–10.
3 Morley CJ, Thornton AJ, Green SJ, Cole TJ. Field trials of the Baby Check score card in general practice. *Arch Dis Child* 1991;**66**: 111–4.
4 Thornton AJ, Morley CJ, Cole TJ, Green SJ, Walker KA, Rennie JM. Field trials of the Baby Check score card in hospital. *Arch Dis Child* 1991;**66**:115–20.
5 Pillo-Blocka F, Jurimae K, Khoshoo V, Zlotkin S. How much is 'a lot' of emesis? *Lancet* 1991; **311**:12.

Dr Morley comments:
I would like to thank Dr Sowden for his interest in Baby Check. I understand his reservations about parents' ability to report their children's symptoms accurately. However, when mothers exaggerate their baby's symptoms one should consider whether they are really incapable of reporting the symptoms accurately or whether they perceive that the doctor is disinterested in their baby's illness unless presented with florid and overt symptoms.

Dr Sowden uses mothers' lack of reliability at assessing the amount of fluid on a wash cloth as an indication of their inability to assess their baby's symptoms. This is a notoriously difficult thing to assess and I would be surprised if doctors could do better.

When assessing a baby's illness the first thing all doctors should do is ask the mother about the baby's symptoms. It is very difficult to come to an accurate diagnosis without taking a history. However, the information obtained is more useful if the mother is asked questions she is likely to be able to answer. For example in Baby Check the mother is not asked the volume of the vomit but, 'Has the baby vomited at least half the feed after each of the last three feeds?'

The research project, from which Baby Check was developed, set out to find the symptoms (reported by mothers) and signs (seen by the assessors) which could be used to grade the severity of a baby's illness. Interestingly, out of all the possible factors which might be considered important and useful, seven of the 19 factors selected by the analyses were symptoms. Despite any inaccuracy in the way these might have been reported by the mothers they were found to contribute significantly to the assessment of a baby's illness.

Although we were concerned that mothers might not be able to use Baby Check two field trials showed that they had few problems with the interpretation of the symptoms or signs. Most people who used Baby Check in our studies found it helpful, particularly if they were inexperienced at assessing babies' illnesses. I would like to suggest that Dr Sowden tries Baby Check with his patients. I think he might be pleasantly surprised to find how well mothers can assess their babies when given a new tool for a difficult task.

Ischaemic brain lesions diagnosed at birth in preterm infants

SIR,—The observation by Sinha *et al*, that nine out of 232 newborn babies showed periventricular echogenicity two hours after birth requires clarification if inferences are to be drawn with regard to the timing of the insult which leads to periventricular leucomalacia.[1] Confusion will exist as long as paediatricians continue to use the terms echogenicity, ischaemia, periventricular leucomalacia, and periventricular cysts as though the terms were synonymous.

Echogenicity from the authors' own observations is reversible, as is ischaemia, for at least some patients. Periventricular leucomalacia with or without cyst formation is as permanent as the disability which it may cause. Periventricular leucomalacia is a particular form of cerebral infarction which becomes cystic only after a few days when sufficient numbers of dead cells have been removed for a cavity to be detectable. Precisely how long this interval is before a cyst is seen is something of an imponderable but is probably of the order of 10 days.

It comes as no surprise that there were nine infants whose brain pathology may have been initiated in the intrapartum or immediate postnatal period. Changing the supply of oxygen from placenta to lungs is bound to be intrinsically hazardous. A more interesting question is how many babies sustained cerebral infarction from a hypoxic or ischaemic episode days before the mother's confinement. Cavitation, as opposed to echogenicity, of the infant brain at two hours postnatal age would be convincing in that respect. The reader is not informed.

The authors make it clear that late onset periventricular leucomalacia is three times more common than early onset cases. It is worth pointing out that this was not the situation that was apparent to perinatal pathologists in the days before ultrasonography existed. Only recently have significant numbers of small babies been kept alive long enough for periventricular cavitation to become manifest either by ultrasound or by direct observation postmortem. For these babies postnatal management is more likely to be relevant to their handicap than antepartum

[redacted]

but as the progression of initial echogenicity to cyst formation takes sometime between seven to 10 days, it seemed quite reasonable to deduce that these changes might have started before or during birth.

The ability to make serial observations of the brain non-invasively by ultrasound has led to a better understanding of the pathogenesis and natural history of ischaemic brain lesions. We agree that these lesions tend to occur mostly in relation to hypoxic-ischaemic injury either at birth or during the neonatal period but similar insults can occur antenatally. This

for the treatment of suspected coagulase negative staphylocci infection in the neonate.

N J SHAW
V DAMJANOVIC
A M WEINDLING
Regional Neonatal Intensive Care Unit,
Department of Child Health,
Liverpool Maternity Hospital,
Oxford Street,
Liverpool L7 7NB

1 Millar MR, Todd N, Mackay P. Neonatal infections with coagulase negative staphylococci. *Arch Dis Child* 1990;**65**:1015–6.

endotoxin damages the cochlea, children with meningococcal disease would be a suitable population to study. Children present predominantly with septicaemia, meningitis, or a mixed picture of septicaemia and meningitis.[3] Deafness in survivors of fulminant septicaemia, meningococcaemia without meningitis, and meningitis alone might be

1 Sharples PM, Storey A, Aynsley-Green A, Eyre JA. Avoidable factors contributing to death of children with head injury. *BMJ* 1990;**300**: 87–91.
2 Crouchman M. Head injury—how community paediatricians can help. *Arch Dis Child* 1990; **65**:1286–7.
3 Sharples PM, Storey A, Aynsley-Green A, Eyre JA. Causes of fatal childhood accidents involving head injury in the Northern region, 1979–86. *BMJ* 1990;**301**:1193–7.

shunting in the acute phase of hyaline membrane disease. *Arch Dis Child* 1991;**66**:6–11.
2 Kitabatake A, Inoue M, Asao M, *et al*. Non-invasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;**68**:302–9.

Drs Evans and Archer comment:

We are grateful to Dr Craig for drawing our

[redacted]

Archives of Disease in Childhood 1991; **66:** 909

should also be expected to be a good research worker has never been explained. These are different jobs requiring different skills and interests. Animal physiologists seeking promotion would look askance if rejected on the grounds that they were poor veterinarians—and yet good clinicians are frequently rejected on the grounds they are poor researchers. No wonder they retaliate by producing a large quantity of second rate work that clogs up the journals. It has been argued that the number of publications is one way of distinguishing one candidate from another in a close field. Why not use another irrelevant measure instead: skill at tightrope walking for instance? This would reduce the present volume of substandard publications, save the time of authors, editors and readers, and

is expensive. There is an instruction manual which is reasonably easy to follow, but I found the introductory video tutorial on how to use the system more helpful. Unfortunately, this video section is being dropped from the new edition, due out soon, to make more use of space on the disc.

There are several main components to the system. The illustrated trait directory is a very useful part. Dysmorphology like all other specialties has its own language, and it is helpful for those new to the discipline to see what exactly is meant by a keel shaped forehead, triangular face, prominent ear crus, camptodactyly, etc. The two main components of the system are the search/diagnostic facility and the listing of features of known syndromes. To initiate a search one has to set up a list of

sections on chromosome abnormalities where the karyotype nomenclature is frankly wrong in many instances. The accuracy of individual diagnoses where a diagnosis relies on phenotype alone is good, but for some disorders rather questionable cases are included and for others the 'blackout' required to preserve anonymity also hides diagnostic features.

POSSUM is designed for use by specialist geneticists and paediatricians as a diagnostic aid and for tutorial assistance for specialists in dysmorphology. As a dysmorphologist my main usage would be in verifying diagnoses and in teaching. It is a marvellous teaching aid for those in training and those trained in other disciplines and its ease of use makes self teaching an option. There are a number of rival systems especially the London Dys-

[redacted]

the ocular compression test is used to confirm a diagnosis of anoxic seizures.

In the remaining chapters the book provides information on other causes of loss of consciousness and ends with a section on the management of fits and faints. There are comprehensive accounts of 'psychic and psychogenic seizures', 'funny turns and funny attacks' and 'fits and faints in a special setting'. Prognosis and management are discussed in general terms with emphasis on the history and clinical findings. Some mention is made about future research in drug treatment.

I welcome this book which stimulates questions about seizure disorders in childhood. It is a useful guide to those seeking a better understanding of such disorders as the information contained will provide insights about a range of conditions associated with loss of consciousness. It will also be a valuable addition to the university library in order to encourage the application of research to the clinical situation.

S W D'SOUZA
Consultant paediatrician and senior lecturer

Pediatric AIDS. Edited by Philip A Pizzo, Catherine M Wilfert. (Pp 813; £56·50 hardback.) Williams and Wilkins Ltd, 1991. ISBN 0–683–06894–6.

It is less than 10 years ago that the first report was published of a child with AIDS from the USA. AIDS in children is now one of the leading causes of death in the USA, is a major contributor to increasing infant mortality in places such as Africa, the Caribbean and some parts of South America, and is now appearing in most countries in the world. This is the first major textbook on paediatric AIDS and comes not surprisingly from the USA. It is written by leading experts in the American field and it is a credit to the editors that they managed to produce this book in such a short period of time, containing as it does so much up to date information.

The value of this book will be twofold. Firstly as a major reference for paediatricians who are directly involved in the field both clinically and from the research aspect (although likely to become out of date quickly in such a fastly changing field, it will be an invaluable summary of knowledge so far).

This is a tome of a book but to be welcomed as the first major book on HIV in children.

DIANA GIBB
Lecturer in infectious diseases

Worldwide Variation in Human Growth. 2nd Ed. Edited by Phylis B Eveleth and James M Tanner. (Pp 397; £25·00 paperback, £60 hardback.) Cambridge University Press, 1991. ISBN 0-521-35916-3 (p/b), 0-521-35024-7 (h/b).

There can be few books which provide such a complete coverage of any scientific subject as this. To present in one volume, in a form acceptable and assimilable to a reader, vast quantities of data from hundreds of growth studies, undertaken in over 40 countries with differing methodology, may seem wellnigh impossible, but the editors have achieved this. The first edition, published in 1976, was a monumental undertaking, and largely the outcome of 10 years of studies under the auspices of the International Biological Programme. Now the editors have repeated their work, achieving the same standard of excellence and admirable presentation. So many new data have been forthcoming since the completion of the previous programme, through more sophisticated and extensive studies from all over the world, that this second edition largely replaces the first. There are only occasional references to the earlier studies when nothing has subsequently superceded them. This volume, which includes all serious studies of child growth from 1974–88, is by far the largest series of growth data ever assembled, and discusses growth in terms of height, weight, skinfolds, limb circumferences, and skeletal diameters.

As in the previous edition the book is introduced by a description of methods and standards for comparative growth studies. In the ensuing six chapters the authors discuss comparisons of growth patterns between races, both in their native environments and following migration to other continents. A further section considers population differences in the rate of maturation as shown by skeletal, dental and pubertal development, and knowledge of these aspects in particular has increased dramatically over these recent years. The

ises in physiological, epidemiological, or clinical aspects of growth.

J M H BUCKLER
Senior lecturer in paediatrics and consultant paediatrician

Developmental Examination of Infants and Preschool Children. By Dorothy Egan. (Pp 84; £15 hardback.) Clinics in Developmental Medicine. Blackwell Scientific Publications, 1990. ISBN 0-632-02844-0.

Like hundreds of other young doctors, I was inspired by the teachings of a small, frail paediatrician in her eighties who exuded a tremendous vitality and enthusiasm for child development. Dorothy Egan, who has been an outstanding clinician and teacher at Guy's Hospital for over 30 years, has now summarised her accumulated experience and wisdom in a short monograph. This book is designed as a practical guide for general practitioners and health visitors involved in preschool surveillance rather than a comprehensive textbook of child development. Its strength lies in the description of the art and style of developmental assessment rather than the minutiae of periodic developmental examinations. This descriptive strength is, however, underpinned by population based research. After many years spent refining simple developmental tests in clinical practice, Dr Egan has standardised them on 425 normal children, and presents the normative data in graphical form.

The book opens with a useful overview of normal development summarising normal stages up to 4·5 years. The best parts of the book include sections on: 'when to worry about children', which gives sensible advice illustrated by case histories, and a short chapter on the craft of developmental examination. These are the areas of developmental assessment which are most difficult to learn, and Dr Egan usefully summarises years of experience.

The second half of the book has chapters on clinical tests of hearing and vision, the assessment of language, performance, and gross motor skills. Written in an abbreviated style, almost in note form, they provide guidance rather than a critical assessment of the strengths and weaknesses of the tests. The best section is the one on language, which includes a detailed description of the Egan bus

[redacted]

note form, the language remains clear and the book is easy to read.

This book joins many others aimed at primary care professionals involved in child health surveillance. It is quite expensive for its size, and a paperback version might prove more popular. It clearly describes a British system of developmental assessment which has been refined over many years, and is the distillation of enormous experience of young children.

It will be of practical use to GPs and health visitors. Trainee paediatricians not lucky enough to have experienced Dr Egan's clinical teaching would also benefit from reading this book and by acquiring the clinical skills it describes.

A MEMOND
Consultant paediatrician
(community child health)

Textbook of Fetal and Perinatal Pathology. Edited by Jonathan S Wigglesworth and Don

[redacted]

range from assessment of fetal growth, the performance of the perinatal necropsy or examination of abortuses and stillborn infants, to congenital tumours, disorders of the immune system, infection, and inborn metabolic diseases. While most chapters provide solid practical guidance, and the presence of innumerable tables of normal values are particularly valuable (down to anal diameters and phallus lengths!), the theoretical background, such as a consideration of the causation of malformation, is not ignored.

The second volume covers all the main organ systems, up to and including eye pathology, and an in depth look at the orofacial region. These chapters appear reasonably comprehensive and, in researching recently arisen problems, have provided either a useful comment or reference. More comprehensive specialist texts will not be replaced of course, particularly in the field of dysmorphology, as the descriptions here will often only be of value if a diagnosis has already been made or suspected.

complimentary to that typically present in more clinical works.

S J GOULD
Consultant paediatric pathologist

A Parent's Guide to Cystic Fibrosis. By Burton L Shapiro and Ralph C Heussner Jr. (Pp 124; $14·95 hardback.) University of Minnesota Press, 1991. ISBN 0-8166-1488-1.

It is likely that the knowledge and competence of parents of children with cystic fibrosis is at least as important a factor in modifying the outlook for the patient as the corresponding knowledge and skills of the clinical consultant. Books explicitly written for parents need to be simple, accurate, up to date, attractive, and informative. The amount of information to include is a matter of judgment, and the authors of this little book have successfully avoided the temptation to show off their medical knowledge by including too much,

SPECIAL BMA MEMBERS EDITION

MIRROR OF MEDICINE

A HISTORY OF THE BMJ

P. W. J. BARTRIP

THE·BRITISH·MEDICAL·ASSOCIATION
MDCCC XXXII

[redacted]

"Days
to remember
... *all my life*"

[redacted]